THE SYNTHESIS OF CHEMOTHERAPEUTIC AGENTS

DERIVED FROM

2:3-BENZ-γ-CARBOLINE AND 2:3:4':3'-QUINOQUINOLINE

by

NORA E. STOREY, B.Sc.

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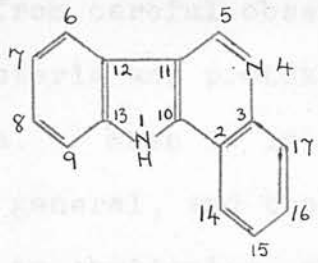
May, 1949.

CONTENTS

SYSTEM OF NUMBERING

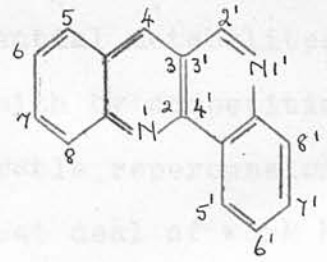
2:3-Benz-γ-carbolines.

The molecule has been numbered in accordance with the system adopted by the Journal of the Chemical Society, namely:



2:3:4':3'-Quinoquinolines.

The numbering of the nucleus used throughout the thesis is shown below:



All new compounds which have been analysed, or of which derivatives have been analysed, are underlined whenever they appear in the text.

INTRODUCTION - HISTORICAL

Chemotherapy is still essentially an empirical science, such few theories as there are having been evolved to explain observations, rather than point the way to fresh discoveries. The classical 'side-chain' and 'chemo-receptor' theories of Paul Ehrlich, for instance, were developed not from any general principle, but from careful observations on the behaviour of bacteria and protozoa towards certain classes of drugs. When it is considered that biochemistry in general, and the biochemistry of micro-organisms in particular, was then only in its infancy, such an attitude is scarcely surprising.

A more rational approach to the study, however, was put forward in 1940 by Fildes. This is based on the idea that many chemotheraputic agents owe their activity to the similarity of their structures to those of essential metabolites, whose metabolism they interfere with by competition. The hypothesis has had considerable repercussions in the antimalarial field, and a great deal of work has been carried out to ascertain the biochemistry of, and essential for metabolites for, the malarial parasite. One of the first observations in this direction was made by Trager (1943), who showed that the survival of

P. Lophurae is favoured by calcium pantothenate. As a result of the work, various analogues of pantothenic acid were synthesised, and tested for antimalarial activity in avian malaria. Of these, pantothenophenone(I)(Woolley, 1944.) was found to show the most promising activity.

$COCH_2NHCOCH(OH)C(CH_3)_2CH_2OH$ I.

Other cultural studies with mammalian parasites in vitro have established glucose, p-aminobenzoic acid, adenine and methionine as essential nutrients for P. Knowlesi, and have pointed the way to a further extension of studies in vivo (Anfinsen et al., 1946; McKee et al., 1947.) Monkeys deficient in ascorbic acid are able to control spontaneously an infection with P.Knowlesi, while the absence of methionine from the diet, and monkeys on fast, will also control this organism; a state of affairs which no longer exists if dl-methionine is given in the diet. (McKee, 1946; McKee and Geiman, 1948.) It will be interesting to see what effect methionine analogues, and other compounds which can accept and donate methyl groups, will have on parasitic growth and multiplication. Already it has been shown by McKee and Geiman (1948) that in vitro growth of P. Knowlesi is markedly inhibited by methoxinine and ethionine, (the higher homologue of methiomine), and that the inhibition is overcome by the addition of extra methionine.

These and other findings, though as yet, they have not lead to any great antimalarial discovery, are of importance in that they should, in the future, guide the worker in this branch of science with greater certainty into more fruitful fields of research. In the meantime, the chemotherapist is driven to the expedient of working more or less systematically over certain fields suggested to him by some vague hint or analogy. This is no easy matter, for despite the combined ingenuity of chemists and biologists during the past half century, it is still doubtful whether the ideal drug for either the prophylaxis or the radical cure of malaria has been discovered. Many compounds have been prepared, indeed thousands have been tested - the American "Survey of Antimalarial Drugs" alone contains over twelve thousand five hundred, and runs into three volumes. Only relatively few of the large number of compounds screened reach the stage of clinical trial, however, for careful and prolonged tests are necessary with all new antimalarial drugs, because of the diversity, not only of the species of plasmodia, but also of the strains.

In order to understand the problem which malaria presents, it is necessary to know something of the life cycle of the malarial parasite. Malaria is a protozoal disease caused by a parasite (Plasmodium) which spends part of its life cycle in certain vertebrates, and part in the anopheline

species of the mosquito. The salient features of the life cycle are as follows: the development of the parasite in the mosquito, the inoculation of sporozoites into the host when bitten by an infected mosquito, the exo-erythrocytic developmental phase of the parasite, and the asexual reproduction of the plasmodium (schizont stage) in the red blood corpuscles of the vertebrate. This last stage causes the cells to burst, and liberate foreign proteins (merozoites) into the blood stream, ~~and~~ bringing on the attacks of fever so characteristic of malaria. In addition to this asexual cycle, the plasmodium can undergo a cycle of sexual reproduction: the parasite in the red blood corpuscle can, when half grown (trophozoites), develop into male and female forms (gametocytes) which, as such, produce no further symptoms to the host. They may, however, be ingested by mosquitos feeding on the blood of a malarial patient, and subsequently complete their sexual life to reproduce sporozoites in the saliva.

The exact fate of the injected sporozoites is still a matter of controversy, but it is important to note, firstly, that Schaudinn's observation (1902) that they penetrate the erythrocytes directly has never been confirmed, and secondly, that there is always a latent period following the bite before parasites can be demonstrated in the blood. The existence of this pre-erythrocytic phase of the

parasite has been demonstrated experimentally in fowls by James and Tate (1937), and more recently in monkeys by Shortt and Garnham (1948). Shortt, Garnham, Covell and Shute (1948) claim to have found pre-erythrocytic forms of P.Vivax in the liver of a patient, though this observation does not appear to have been confirmed. These exo-erythrocytic forms may clearly serve as a reservoir from which blood forms are continually being released; and if indeed this happens, it is a sound explanation as to why we fail to achieve cures when we use drugs which are active only against blood forms.

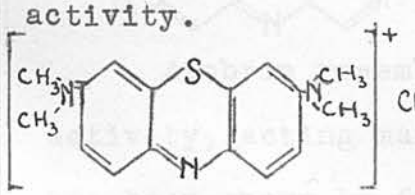
From what has been said, it will be apparent that there are at least five possible targets in the control of malaria; namely, the mosquito, the sporozoite, the exo-erythrocytic forms, the schizont and the gametocyte.

Entomological attacks on the mosquito have been by studying, and attempting to alter, its environment. This has met with considerable success, particularly where the destruction of swamps and stagnant water has abolished the permanent haunts and breeding places of the species. The use of insecticides, still in its experimental stage, has already proved valuable in limited areas. D.D.T. smoke, put down from the air, has been employed with success in campaigns for the complete eradication of the mosquito from island areas, and Gammexane has proved useful in the destruction of adult mosquitos in houses and plant-

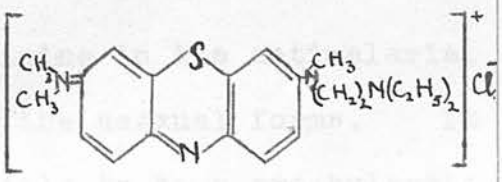
ations. Nevertheless, it can scarcely be expected that insecticides will be a practicable, or economic way of tackling a mosquito belt of thousands of square miles of unoccupied territory.

A search for drugs to kill the sporozoites, or the exo-erythrocytic forms - that is, a search for causal prophylactic drugs - was largely neglected during the early work on the chemotherapy of malaria in favour of drugs to alleviate the clinical symptoms of the disease - that is, to act on the blood phase. Hence it is seen why quinine (primarily a schizonticidal agent) was the great specific in malaria, and why early experimental chemotherapy centred round the chinchona alkaloids.

The shortage of quinine in Germany during the the war of 1914-1918 stimulated the search for a synthetic substitute, and working on an observation by Ehrlich that methylene blue II showed antimalarial properties, Schülemann, Schönhöfer and Wingler (1932) prepared a compound III, which when tested by Roehl's new and precise canary test showed considerable activity.



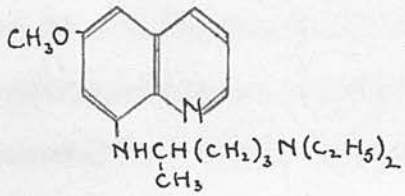
II.



III.

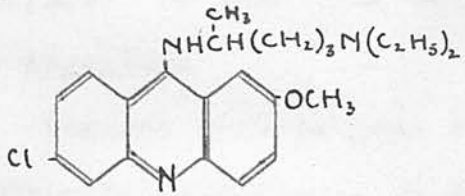
This compound is a dyestuff, however, and so similar experiments were carried out using quinoline in the place of the methylene blue nucleus. The

culmination of this work resulted in the discovery of plasmoquin IV , a drug which attacks the gametocytes and to some extent the asexual forms of the parasite. Its antimalarial activity is high, but at the same time it is very toxic, and is to be regarded as a complement to, rather than a substitute for, quinine - quinine acting on the asexual cycle, that is, on the schizonts.



IV

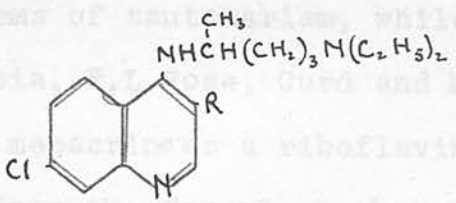
In order to reduce the toxic effects of plasmoquin, other heterocyclic ring systems were sought, and based no doubt on Browning's exploitation of acriflavin during the first World War, the acridine nucleus was examined and condensed with the plasmoquin side chain, to give eventually the antimalarial atebrin, now known as mepacrine V . (Mauss and Mietzch, 1933.)



V

Atebrin resembles quinine in its antimalarial activity, acting mainly on the asexual forms. It has been shown by field trials to be a prophylactic against benign and malignant malarias, and a cure for the malignant tertian form, It has, however, unfortunate properties, causing colouration of the skin and gastro-intestinal disturbances.

Following the discoveries of plasmoquin and mepacrine, a large amount of chemical synthetic work was carried out all over the world, concerned in the main with derivatives of acridine and quinoline. A number of compounds having antimalarial activity were described, and of these several are derivatives of 4-aminoquinoline. The most important of the series is chloroquine or resochin (VI), 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline (R=H), and sontochin ($R=CH_3$), the 3-methyl derivative of chloroquine.



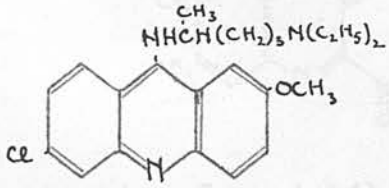
VI.

These drugs have an activity of the same order as mepacrine, but are relatively non-toxic and are colourless, so that they do not stain the skin as does mepacrine.

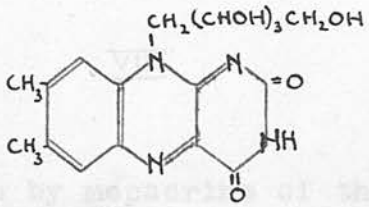
Various workers have attempted to build up antimalarial structures on other heterocyclic nuclei; thus phenanthrolines, benzquinolines, pyridoquinolines, quinazolines, carbazole and other ring systems have all received attention, and in certain cases activity was achieved. The guiding principle in most of this work was the idea made use of by Schülemann, Schönhöfer and Wingler, and which led to the synthesis of plasmoquin; namely, that by linking

a suitable basic residue to an amino group in a heterocyclic ring system, antimalarial activity against avian malaria might result.

A great deal of speculation as to why this should be, arose as a result of this work. Magidson and Grigorowsky (1936) suggested that the basic side chain aided absorption of the molecule into the parasite body, where the parasiticidal part - identical with the substituted nucleus - brought about the real toxic effect. Schönhöfer, on the other hand, speculated in terms of tautomerism, while others again, Medinaveitia, F.L.Rose, Curd and Mosher among them, postulated mepacrine as a riboflavin antagonist. As will be seen from the formulae, there is a general structural resemblance between the two compounds.



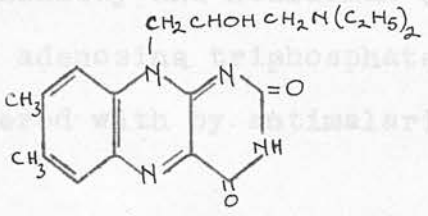
Mepacrine



Riboflavin

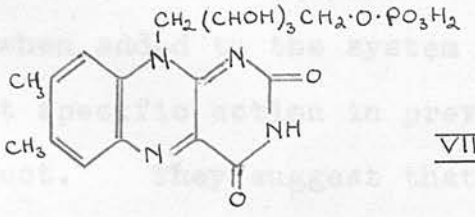
In support of the theory, Medinaveitia (1946) showed that the growth inhibitory action of mepacrine for L.Casei is antagonised by riboflavin. This theory cannot be accepted without modification, however, for it was found by Mosher, who prepared a compound (VII) resembling riboflavin even more closely than mepacrine, and yet containing the antimalarial basic side chain, that the substance was devoid of anti-

malarial activity (Mosher 1946)



VII.

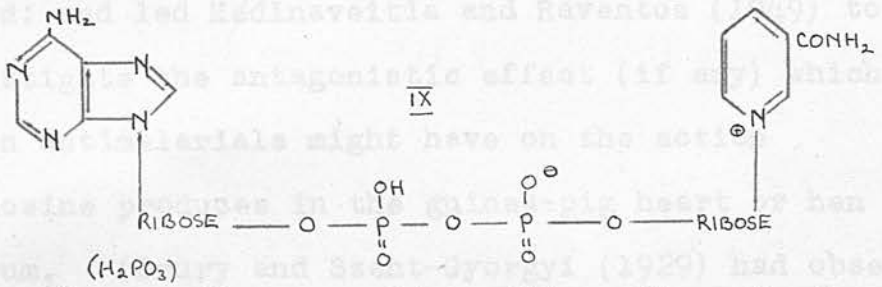
The work of Haas (1944) also lends credence to the idea. This worker was concerned not with living organisms but with isolated enzyme systems, and he found that cytochrome reductase (alloxazine mononucleotide - protein) was inhibited by mepacrine, but that this inhibition was antagonised by adding an excess of the flavin-containing prosthetic group (VIII) in a manner suggesting competition. On the other



VIII

hand, protection from inhibition by mepacrine of the glucose-6-phosphate dehydrogenase could be afforded by the triphosphopyridine nucleotide prosthetic group (IX), a compound which bears no structural relationship to mepacrine. This antagonism is found not only with mepacrine, but is also shown with quinine and quinoline bases, none of which resemble any portion of the coenzyme molecule. In this case, however, the antagonism may be due to the adenylic acid part of the molecule and in this, may bear

some relation to the suggestion put forward recently by Bovarnick, Lindsay and Hellerman (1946), that the utilisation of adenosine triphosphate or adenylic acid is interfered with by antimalarial drugs.



IX

These authors, working with erythrocyte-free malarial parasites, observed that plasmodia previously deprived of glucose, oxidise this substance only after an induction period, and that in the presence of atebrin, quinine or plasmoquine, the oxygen uptake is then strongly inhibited (78-95%). A.T.P. or adenylic acid, when added to the system, were found to exert an almost specific action in preventing this inhibitory effect. They suggest that the induction period is related to the necessity for the phosphorylation of glucose before the substrate can be utilised, and that the antimalarial drugs interfere with phosphorylation, possibly by competition with A.T.P. or adenylic acid. The possibility cannot be excluded, however, that the basic drug is actually combining with the acidic A.T.P. or adenylic acid, and thus removing them from the system.

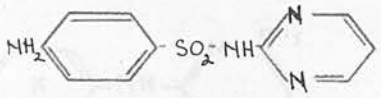
This hypothesis, that interference with an

adenosine-containing enzyme system, might result in antimalarial activity, has led to the preparation of several active antimalarial compounds by Hull and Todd (1946; 1947.), mainly in the alkylpyrimidine field; and led Médinaveitia and Raventos (1949) to investigate the antagonistic effect (if any) which known antimalarials might have on the action adenosine produces in the guinea-pig heart or hen caecum. (Drury and Szent-Gyorgyi (1929) had observed that adenosine when injected intravenously into an anaesthetised guinea-pig produces an auriculo-ventricular block.) Médinaveitia and Raventos found that this particular action of adenosine is, in fact, antagonised by most antimalarial drugs, the intensity of the antagonism being proportional to their antimalarial activity, as measured against P. Gallinaceum in chicks. This antagonistic effect of the antimalarial drugs on the phenomenon adenosine produces in the guinea-pig heart, is thus in conformity with the idea that antimalarial action may be dependent upon some interference with the biochemical functioning of adenosine and adenosine-containing compounds. It is interesting to note in this connection that Speck and Evans (1945) found that hexokinase, catalysing the phosphorylation of glucose

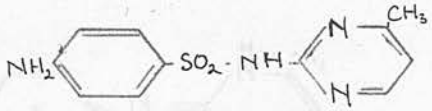
by A.T.P., was notably sensitive to the action of mepacrine when isolated from the malarial parasite, though the same enzyme system, isolated from other tissues, showed less sensitivity to the drug. If confirmed, this may well prove to be of outstanding importance in the search for a "therapia sterilisans magna".

However, be that as it may, it is quite obvious that had any one of these suggested working hypotheses been followed unremittingly, we might have had a number of extremely interesting compounds, chemically, but we should not have had paludrine. Paludrine developed not from any definite chemotherapeutic theory, but from an intuitive feeling that it might be advantageous to build up antimalarial drugs on the basis of some ring system of biological importance. The choice of Curd and Rose of I.C.I.Ltd., Blackley, fell on the pyrimidine ring system for two reasons. Firstly, because pyrimidine derivatives are of great physiological importance, and as components of nucleoproteins they take part in a number of life processes. The chance that analogues of these essential constituents might interfere with growth of the parasites, in the way that sulphonamides interfere with the utilisation of p-aminobenzoic acid by certain bacteria, seemed worthy of investigation. Secondly, among the sulphonamide drugs tested for antimalarial properties sulphadiazine ($\overline{X}$) and

sulphamerazine (XI), both containing a pyrimidine nucleus, showed promising activity (Coggeshall, 1941).

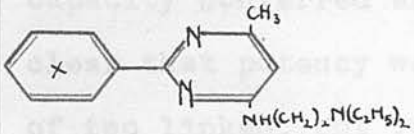


X

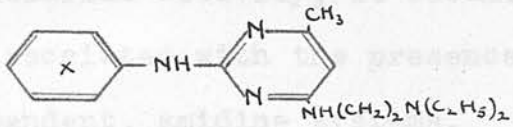


XI

Consequently, compounds of the type (XII) were prepared and found to be inactive; though subsequently, when derivatives of the anilinopyrimidines (XIII) were investigated, activity was immediately encountered.

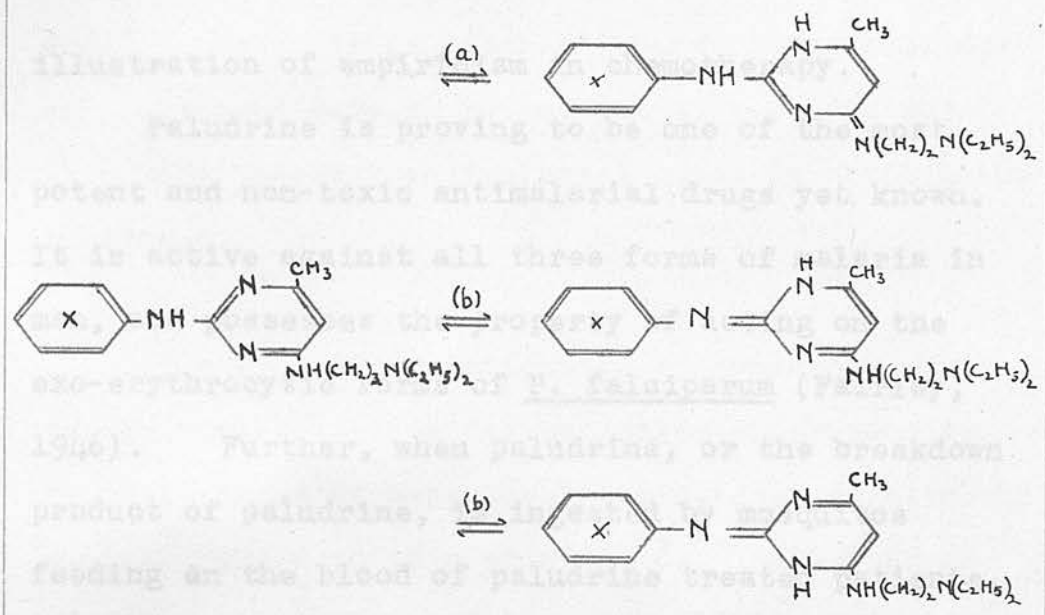


XII

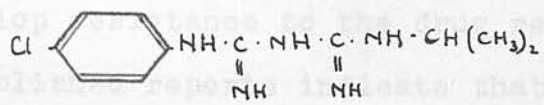


XIII

Consideration of the above two formulae led to the conclusion that it was desirable to link the aryl and pyrimidine nuclei by a grouping capable of prototropic change; for it is to be noted that as well as being capable of the type of tautomerism (a) suggested by Schönhöfer (1942) originally in connection with mepacrine, compounds of type (XIII) are capable of undergoing tautomerism (b) by virtue of the imino link separating the benzene and the pyrimidine nucleus. With type (XII), (inactive), this interchange is impossible.



Working on the hypothesis that this tautomeric capacity conferred antimalarial activity, it became clear that potency was associated with the presence of two linked, but independent, amidine systems. Eventually, the pyrimidine ring was found to be unnecessary, and a biguanide with high activity was prepared and given the name 'Paludrine'. (XIV)



XIV

It is interesting to note that in 1939, Lourie and Yorke observed antimalarial activity in the diamidine 1:11-undecanediamidine, a compound completely distinct from any antimalarial then known. Had this lead been followed up, it is not inconceivable that paludrine might have been arrived at from an entirely different viewpoint - yet another

illustration of empiricism in chemotherapy.

Paludrine is proving to be one of the most potent and non-toxic antimalarial drugs yet known. It is active against all three forms of malaria in man, and possesses the property of acting on the exo-erythrocytic forms of P. falciparum (Fairley, 1946). Further, when paludrine, or the breakdown product of paludrine, is ingested by mosquitos feeding on the blood of paludrine treated patients. development of the sexual forms of the parasite in the insect is prevented, thus sterilizing the mosquito.

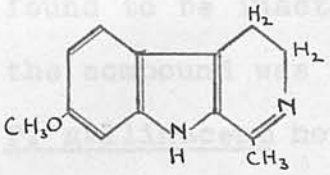
Unfortunately, resistance to paludrine develops readily in avian malaria (Bishop and Birkett, 1947; Williamson, Bertram and Lourie, 1947.), and persists after transmission of the parasite through the mosquito. How far the human malaria parasite will develop resistance to the drug remains to be seen; unpublished reports indicate that the phenomenon may have already arisen. Apart from this difficulty of induced resistance, there are also indications that certain strains of malaria may not be as efficaciously treated as others by paludrine. When, in addition, it is recalled that paludrine is not a causal prophylactic against infection with P. vivax (as contrasted with P.falciparum), it will be seen that the ideal antimalarial has still to be discov-

ered. Hence it is, that in spite of the considerable advances made in recent years, a search for even more powerful antimalarial drugs is still being continued.

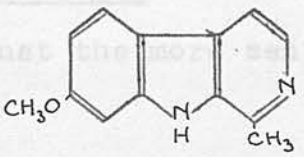
The present investigation was undertaken with the object of testing the antimalarial properties of derivatives of heterocyclic ring systems, hitherto almost untried in this connection. A number of amines, derived from 2:3-benz-γ-carboline and 2:3:4':3'-quinoquinoline, have been prepared and will be tested for antimalarial and general pharmacological activity. Some quaternary salts were also made with a view to trypanocidal action. Derivatives of 2:3-benz-γ-carboline and 2:3:4':3'-quinoquinoline were considered of interest because these compounds carrying a basic side chain would resemble the 4-aminoquinoline type of drug, and, in addition, their chemical properties require elucidating.

Historically, alkaloids carrying a carboline ring system were under examination by James Gunn in the period 1909 to 1911. He, while investigating the pharmacological action of harmaline (XV) and harmine (XVI) in frogs and various mammals, observed that these alkaloids exert a general toxic action on living protoplasm. He concluded that as pharmacological agents, harmaline and harmine

ought to be grouped with quinine, that is, with substances classed as protoplasmic poisons. From this similarity between quinine and the harmala alkaloids, Gunn was led to anticipate a corresponding resemblance in their therapeutic effects. He accordingly tried both harmaline and harmine against human malaria in India in 1919.



XV

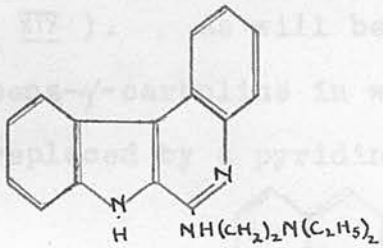


XVI

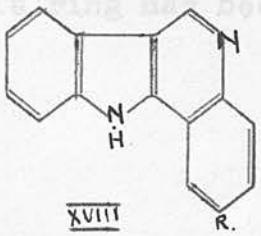
The results were good, especially when it was observed that harmine prevented relapses in all cases tried. Later workers were unable to confirm the results, however, or to obtain any activity against avian malaria with harmaline or harmine, or with various synthetic analogues. (Goodson, Henry and Macfie, 1930; Coulthard, Pyman and Levene, 1933; Konowalowa and Orechoff, 1934.)

Nevertheless, the original experiments of Gunn cannot be ignored, and if we remember that plasmoquine, mepacrine and paludrine were all developed from practically inactive compounds, it is possible that suitable derivatives of carboline, the ring system underlying the harmala alkaloids, might prove effective. In particular, the presence of a basic side chain such as that present in plasmoquine and

mepacrine might lead to a heightening of activity. Kermack and Tebrich (Ph.D Thesis, Edinburgh, 1939.), working along these lines, synthesised a number of such compounds - derivatives of β-carboline and 4:5-benz-β-carboline with a basic side chain in position 2. One such compound was 2-diethylamino-ethylamino-4:5-benz-β-carboline (XVII), which was found to be inactive against P. relictum in canaries; the compound was not tested against the more sensitive P. gallinaceum however.

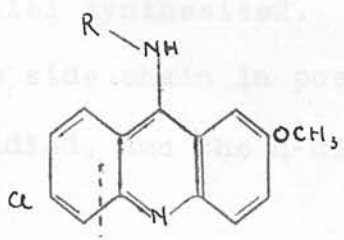


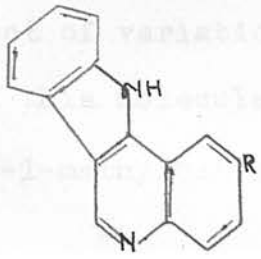
XVII



XVIII

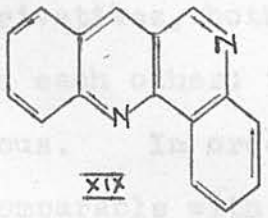
Nevertheless, activity might be expected from a compound of type (XVIII), for this more closely resembles the chloroquin structure, in that the molecule may be regarded as a quinoline derivative with a substituted amino group in its 4-position. The structure may even be considered as related to mepacrine, one benzene ring of which has opened and hinged over to join up with the side chain in the manner indicated.





Consequently, it was considered of interest to synthesise 2:3-benz-γ-carboline, and from it to prepare the bases 1-diethylaminoethyl-2:3-benz-γ-carboline and 4-diethylaminoethyl2:3-benz-γ-isocarboline. Also, because of the apparent importance of chloro- and methoxy-groups in many antimalarial compounds, a number of derivatives of 2:3-benz-γ-carboline have been prepared having these substituents.

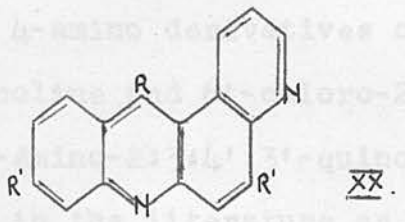
Work has also been carried out on a closely related ring system, namely 2:3:4':3'-quinoquinoline (XIX). As will be seen, it may be regarded as a benz-γ-carboline in which the pyrrole ring has been replaced by a pyridine ring.



XIX

The system is of interest in that it is a bis-quinoline, and as such resembles the pyridoacridine series of drugs. This latter type of compound has been investigated by Dobson and Kermack (1946), Hutchison and Kermack (1947) and Dobson, Hutchison and Kermack (1948), who found that, of the compounds prepared by them, the 3:4:2':3'-pyridoacridine ring system (XX) was the most active of the nuclei synthesised. The effect of variations in the side chain in position 5 of this molecule was studied, and the 4-diethylamino-1-methylbutylamino-

was found to be among the most potent in P. gallinaceum infections in chicks. The introduction of a chlorine atom into both the 2- and 8-positions also appeared favourable for activity, since 2:8-dichloro-(5-diethylaminopropylamino-)-3:4:2':3'-pyridoacridine (XX) was the most active compound obtained by these workers.



$R = NH(CH_2)_3N(C_2H_5)_2$
$R' = Cl.$

XX.

An examination of formulae (XIX) and (XX) shows that as well as both compounds being quinoquinoline derivatives, both carry their nitrogen atoms para to each other; the two series thus appear to be analogous. In order to prepare a derivative of (XIX), comparable with (XX), carrying a basic side chain para to one of the nitrogen atoms, it was considered important to prepare 4-chloro-2:3:4':3'-quinoquinolines and to replace the chlorine atom with an appropriate side chain. In this way compounds of type (XIX) were synthesised.

It has been shown that antibacterial activity in the acridine series is proportional to the extent of cationic ionisation at pH 7 (Albert et al.,1945.). This same relationship holds in the benzquinoline, benzacridine and phenanthridine series, particularly

in the case of amino derivatives which are obtained by the replacement of activated chlorine. These have electronic configurations favouring ionic resonance, making them stronger bases than their isomerides. (Albert and Goldacre, 1943; Albert, Goldacre and Phillips, unpublished reports.) In view of this, it was considered of interest to prepare the 4-amino derivatives of 6'-methoxy-2:3:4':3'-quinoquinoline and 6'-chloro-2:3:4':3'-quinoquinoline. 4-Amino-2:3:4':3'-quinoquinoline (SN 10,077) is reported in the literature as having been tested for antimalarial activity (Survey of Antimalarial Compounds, vol. 2, part 2, p. 1386.); it was found to be inactive against P. gallinaceum infections in chicks, and no chemical data are available as to its method of preparation.

In addition, several methiodides have been prepared from bases of both the benz-γ-carboline and quinoquinoline type. These will be of interest in the trypanocidal field, as they contain two nitrogen atoms which are each para- to a secondary amino group, in which sense they are not unlike 'Antrycide'.

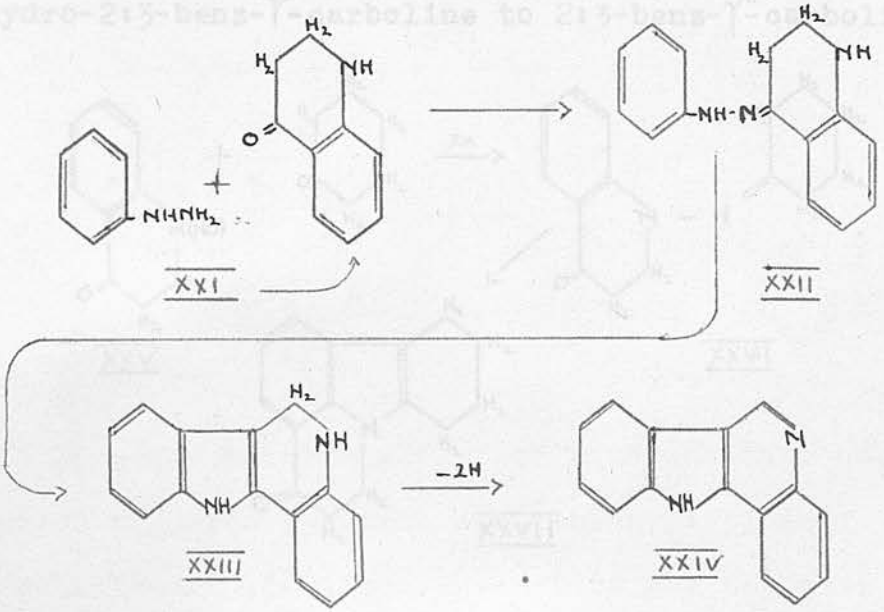
INTRODUCTION — CHEMICAL

As was mentioned in the previous section, certain points in the chemistry of the quinoquinoline and benz-γ-carboline systems require elucidating, and one problem which presented itself was the identity of 2:3-benz-γ-carboline with two compounds claimed to be such by Perkin and Clemo in 1924, and by de Diesbach, de Bie and Rubli in 1934.

The former authors, investigating the properties of 4-tetrahydroquinolone (XXI), found that it combined readily with phenylhydrazine, and that the phenylhydrazone (XXII) on treatment with 20% sulphuric acid underwent the Fischer indole transformation. The resulting compound formed irregular, colourless prisms when crystallised from methanol, in which solvent it showed a light, reddish-blue fluorescence. It melted with sublimation above 320°. The base had a formula $C_{15}H_{10}N_2$, and not $C_{15}H_{12}N_2$, which would be that of the dihydro-2:3-benz-γ-carboline (XXIII) to be expected, if simple cyclisation had occurred.

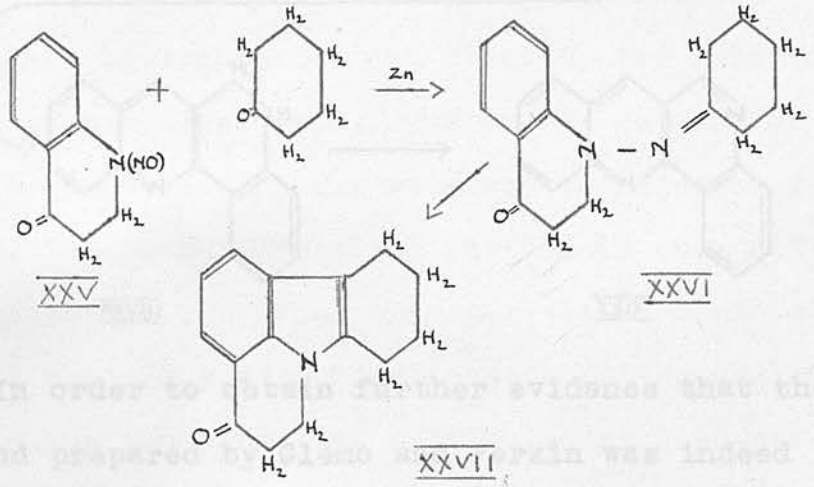
Clemo and Perkin concluded that, instead of cyclising normally with the formation of a dihydro-derivative, the compound had undergone simultaneous oxydation. The resulting strongly basic product (XXIV) 2:3-benz-γ-carboline, was called by the authors

3:4-quinindoline, because it was isomeric with ordinary quindoline (2:3-quinindoline).



The loss of the hydrogen atoms is interesting and rather surprising, especially in the light of a somewhat similar reaction carried out on the N-nitroso derivative of 4-tetrahydroquinolone (XXV) (Perkin and Clemo, 1924.). This compound is converted, on reduction with zinc dust in the presence of cyclohexanone, into 1-cyclohexylideneamino-4-tetrahydroquinolone (XXVI), which on warming with dilute sulphuric acid (20%) readily undergoes the Fischer indole change with the formation of tetrahydrocarbazole-9:8-anhydropropionic acid (XXVII). This compound, although it is not fully aromatic, and the reaction is therefore not quite comparable, is nevertheless still in its reduced form. This would indicate a relative stability on the part of the

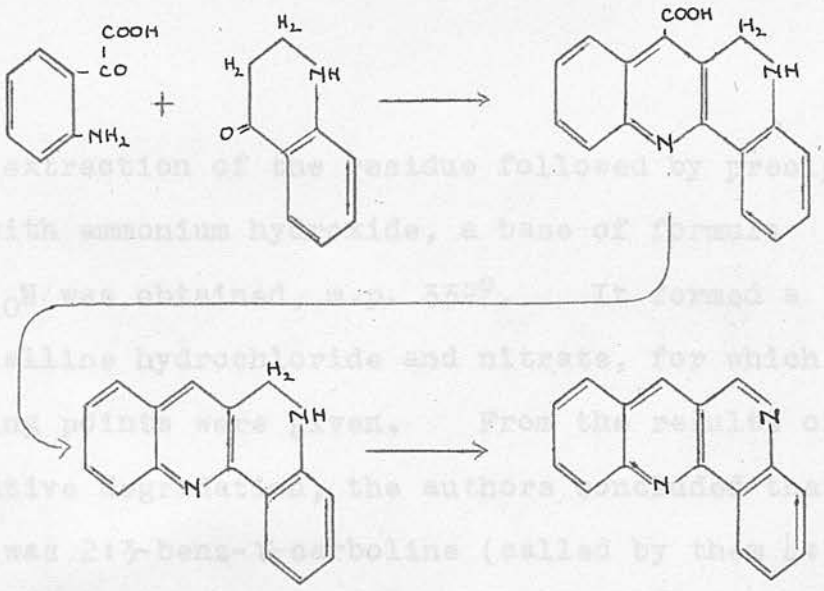
hydrogen atoms to the reagent (20% sulphuric acid) used, and which was alleged to have oxidised the dihydro-2:3-benz-γ-carboline to 2:3-benz-γ-carboline.



XXV XXVI XXVII

Yet another example would indicate the stability of these hydrogen atoms in the 4-hydrotetraquinolone molecule. If it is condensed with isatin at 210° under pressure, carbon dioxide is eliminated, and a base is formed which is evidently dihydro-2:3:4':3'-quinoquinoline (XXVIII). This has to be distilled over lead oxide before it loses two atoms of hydrogen to become 2:3:4':3'-quinoquinoline (XXIX), a case which is more nearly allied to the benz-γ-carboline formation.

It is indeed remarkable that if dehydrogenation did occur in the case of the formation of benz-γ-carboline, it did not occur in the analogous quinoquinoline preparation.



XXVIII XXIX

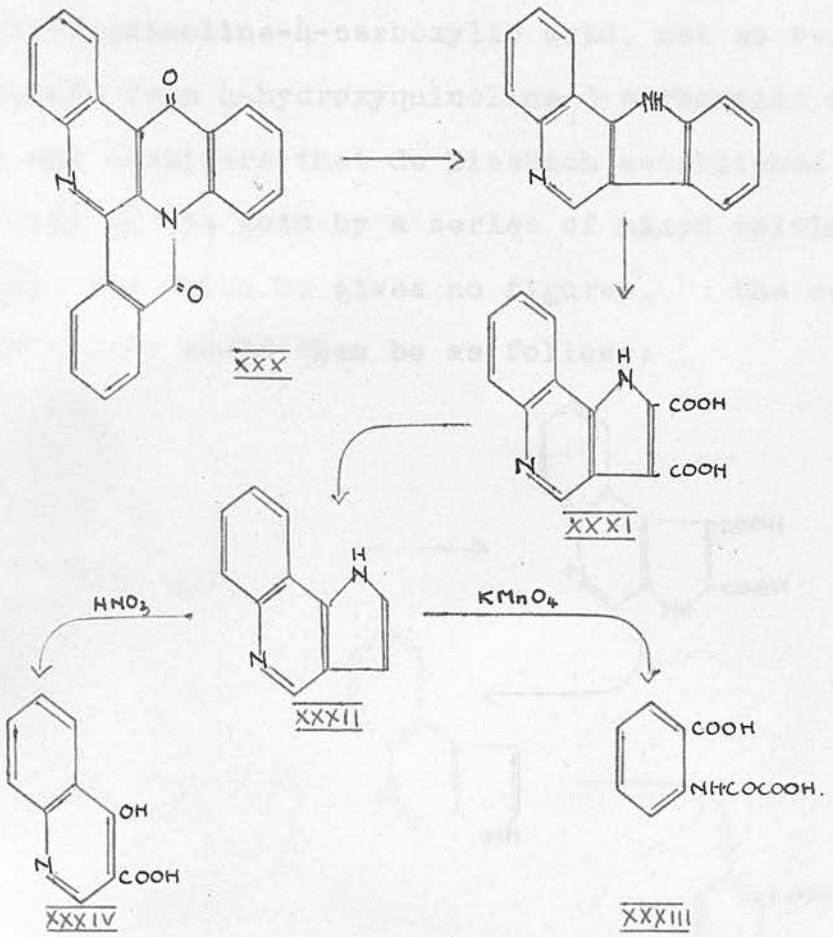
In order to obtain further evidence that the compound prepared by Clemo and Perkin was indeed 2:3-benz-γ-carboline, the literature was searched to see whether a compound of this structure had been made by any other method. Only one other mention of the base is recorded, and though it agrees in properties and melting point with Perkin and Clemo's base, its preparation was again somewhat ambiguous. In this instance, de Diesbach, de Bie and Rubli (1934) claimed to have isolated the compound from the alkaline fusion of Ciba Yellow, a dyestuff which was thought to have formula (XXX). A recent paper by de Diesbach (1948) however, casts some doubt on the structure, though no alternative constitution was suggested.

De Diesbach, de Bie and Rubli found that when Ciba Yellow (indigo yellow) is treated with caustic soda and subjected to a temperature of 300-320°, it is decomposed into various substances. By the

acid extraction of the residue followed by precipitation with ammonium hydroxide, a base of formula $C_{15}H_{10}N$ was obtained, m.p. 332°. It formed a crystalline hydrochloride and nitrate, for which no melting points were given. From the results of oxidative degradation, the authors concluded that the base was 2:3-benz-γ-carboline (called by them 4:3-indoloquinoline). When oxidised with chromic acid the base yielded a dicarboxylic acid ($C_{13}H_8O_4N_2$) (XXXI), which on heating above its melting point lost carbon dioxide to give a white powder ($C_{11}H_8N_2$), soluble in all organic solvents and dilute acids. This compound was considered to be 3:4:3':2'-pyrroloquinoline (XXXII), which when oxidised with permanganate gave oxalylanthranilic acid (XXXIII); and with nitric acid 4-hydroxyquinoline-3-carboxylic acid (XXXIV). The isolation of these products established the existence of a quinoline ring, and the position of the pyrrole structure in the compound $C_{11}H_8N_2$.

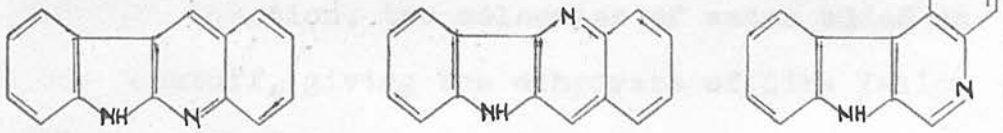
Although this base of de Diesbach agrees in properties with the compound Clemo and Perkin prepared, in that both form crystalline hydrochlorides and nitrates (for which no melting points were quoted by either workers), and both sublime at approximately the same temperature - de Diesbach's at 332° and Clemo and Perkin's above 320° - there is no conclusive evidence that either of these compounds is definitely

2:3-benz-γ-carboline.



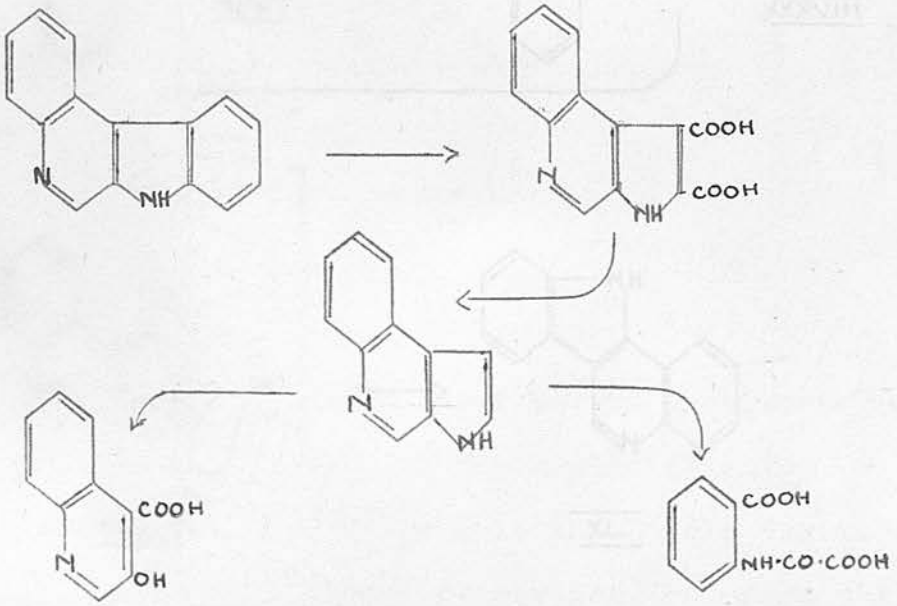
XXX XXXI XXXII XXXIV XXXIII

De Diesbach, for example, although he discredits the idea that his compound might be 4:3-benz -α- carboline (XXXV), or 4:3-benz-δ-carboline (XXXVI), does not appear to have considered the possibility that it might be 4:5-benz-β-carboline, (XXXVII).



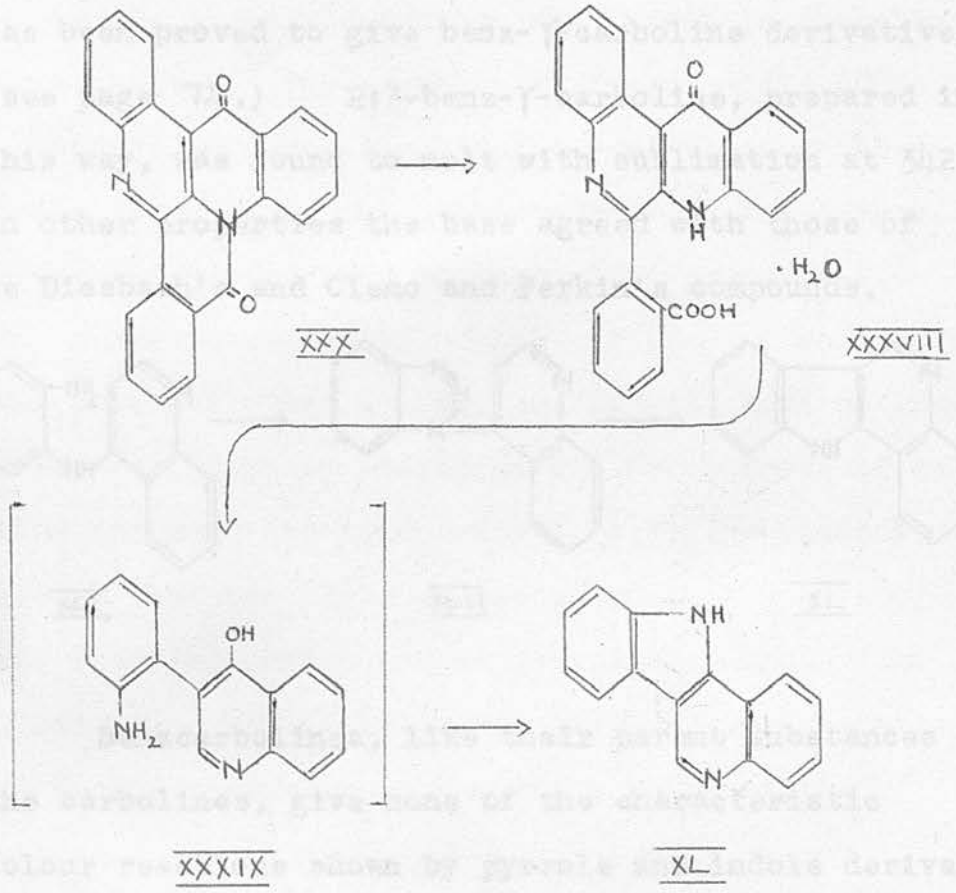
XXXV XXXVI XXXVII

If this were the case, the final degradative products would be oxalylanthranilic acid as before, and 3-hydroxyquinoline-4-carboxylic acid, not so very different from 4-hydroxyquinoline-3-carboxylic acid, when one considers that de Diesbach established the identity of his acid by a series of mixed melting points, for which he gives no figures. The series of reactions would then be as follows:



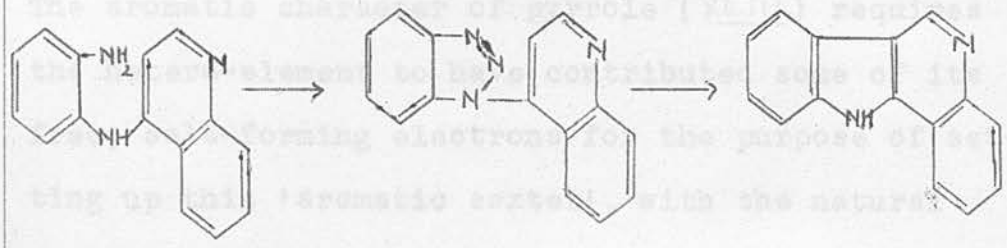
One can easily see how by the hydrolysis of Ciba Yellow with the elimination of benzoic acid, 4:5-benz-β-carboline might be formed, but the explanation for the formation of 2:3-benz-γ-carboline is somewhat more obscure. De Diesbach postulated that during the reaction, two molecules of water added on to the dyestuff, giving the dihydrate of Ciba Yellow (XXXVIII). This was then attacked by the alkali to give phthalic acid and the intermediate (XXXIX),

which condensed internally to give 2:3-benz-γ-carboline. (XL).



The melting point of 4:5-benz-β-carboline is known to be 245° (Lawson, Perkin and Robinson, 1924), which gives weight to the suggestion that de Diesbach's base is in fact 2:3-benz-γ-carboline (332°). To settle the matter conclusively, it was decided that only a direct synthesis of 2:3-benz-γ-carboline could confirm the identity of both de Diesbach's and Clemo and Perkin's bases. This has now been accomplished by the application of the Graebe-Ullmann carbazole

synthesis to the benztriazole (XLII) derived from 4-o-aminophenylaminoquinoline (XLI), a method which has been proved to give benz-γ-carboline derivatives. (see page 72.) 2:3-benz-γ-carboline, prepared in this way, was found to melt with sublimation at 342°; in other properties the base agreed with those of de Diesbach's and Clemo and Perkin's compounds.

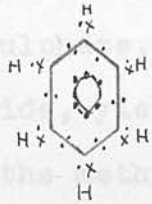


XLI XLII XL

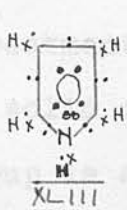
Benzcarbolines, like their parent substances the carbolines, give none of the characteristic colour reactions shown by pyrrole and indole derivatives. They exhibit basic properties, and form well-defined salts with mineral acids. They also give quaternary salts with reagents such as methyl iodide and dimethyl sulphate, which may then be converted into anhydronium bases by the addition of alkali. Since the preparation of such bases appears in this thesis, a short discussion of the theory of this most interesting aspect of carboline chemistry will be included here.

Consideration of quantum mechanics has led to the view that in benzene the carbon atoms are joined

by paired electrons with opposite spins, as in a normal covalent bond, and that the remaining six spare electrons are mobile, and belong to the ring as a whole. The presence of these mobile (π) electrons modifies the behaviour of those in the bonds, shortening the distance between the carbon atoms and giving rise to 'aromatic' properties. The aromatic character of pyrrole (XLIII) requires the hetero-element to have contributed some of its free, salt-forming electrons for the purpose of setting up this 'aromatic sextet', with the natural result that the basic character of this substance has been suppressed, or largely diminished. In pyridine, (XLIV), however, the sextet can be attained without the help of the 'lone pair' on the nitrogen atom.



XLIII

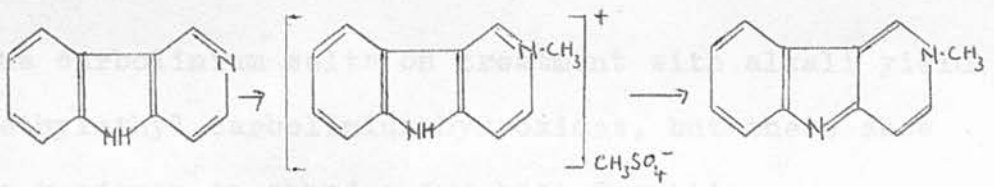


XLIV

From this, it will be seen that in the carboline and benzcarboline molecules, containing both a pyrrole and a pyridine ring, the nitrogen atom in the pyrrole ring will be practically devoid of basic properties, whilst the nitrogen atom in the pyridine ring will be responsible for the basic character of

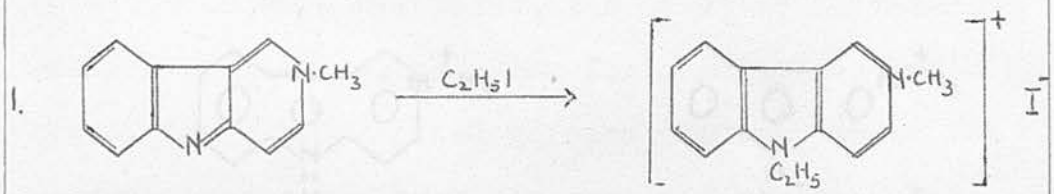
the molecule. Carbolines do, in fact, react readily with dimethyl sulphate to form methosulphates, and with methyl iodide, methiodides. When a solution of the metho-salt is treated with strong alkali, a product is formed having the composition of a methylcarboline. This product may be regarded as being formed from the methohydroxide by the loss of a molecule of water, and is termed an anhydronium base, since it is an 'anhydro' derivative of an 'onium' hydroxide.

Anhydronium base formation is best explained by the consideration of a particular example. γ-Carboline (XLV) reacts with methyl sulphate to form a methosulphate (XLVI), and from what has been said, it is obviously the nitrogen atom in the 4-position which is attacked. A solution of the methosulphate, on treatment with strong potassium hydroxide, yields a solid of formula (XLVII). Since the methyl group is attached to the N_4 position and there is no longer any hydrogen on N_1, the compound is a derivative, not of carboline, but of the hypothetical isocarboline.



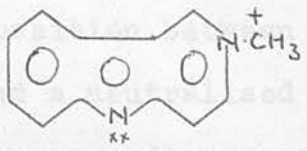
XLV XLVI XLVII

4-Methyl-γ-isocarboline (XLVII) imparts an alkaline reaction to water, with which it evidently unites to regenerate the carbolinium hydroxide; that is, it adds on a proton at the pyrrole nitrogen to form a carbolinium cation. Similarly, 4-methyl-γ-isocarboline will react with ethyl iodide to yield a methylethyl derivative, and 4-ethyl-γ-isocarboline, when treated with dimethyl sulphate followed by conversion of the resulting methosulphate to the iodide, yields an ethylmethyl derivative. These two isomeric compounds are both methylethyl carbolinium salts, but are not identical, showing that the second alkyl group has not attached itself to N_4, but of necessity to N_1. Thus in the isocarbolines, it is the nitrogen atom N_1 which has basic properties.

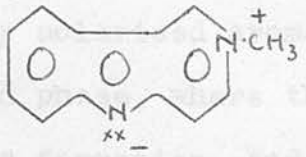


The carbolinium salts on treatment with alkali yield methylethyl carbolinium hydroxides, but these show no tendency to ahhydronium baae formation.

The formulation of anhydronium bases requires some discussion, as will be seen from the consideration of 4-methyl-γ-isocarboline. This compound, as we have seen, is formed from the methyl carbolinium hydroxide by loss of water, or more precisely, from the methyl carbolinium cation by the loss of a proton. If we formulate the carbolinium cation as (XLVIII), where the circles in the ring symbolise the view that the π electrons in each ring produce a stable association, which is responsible for the 'aromatic' character of the substance, then all the rings are 'aromatic' in character. N_1 has its two free electrons taken up in the sextet, and reducing its basicity, whilst N_4 is quaternary and has no free electrons.



XLVIII

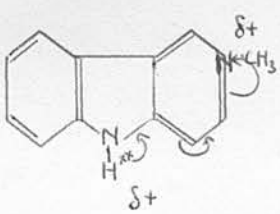


XLIX

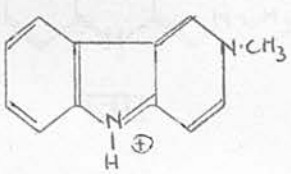
The removal of a proton from N_1 leaves (XLIX), which has now two free electrons on this nitrogen, electrons which are not required for sextet formation and which render the nitrogen negative, and capable of salt formation. Hence it is seen why in anhydronium bases such as 4-methyl-γ-isocarboline, the basic centre is at N_1. This representation

though satisfactory in that all the rings are aromatic, is unstable because the molecule is a dipole.

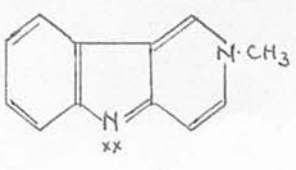
Further consideration of the problem shows that in the carbolinium ion, a considerable shift of the two free electrons on N_1 towards the pyridine ring system with its positively charged nitrogen atom might be expected to occur, giving an electromeric form such as (L), and ultimately (LI), where the positive charge is not on N_4 but on N_1. If then we regard a proton as being removed not from (XLVIII) but from (LI), we obtain (LII). Here the molecule is unstable because the pyridine ring is not aromatic, though neither nitrogen atom carries an electric charge. It was originally suggested by Armit and Robinson (1925) that a complete representation of an anhydronium base occupies an intermediate position between the fully polarised aromatic phase, and a neutralised quinonoid phase, where the tendencies towards aromatic sextet formation, and to neutralisation of the charges, working in opposite directions, reach some compromise.



L



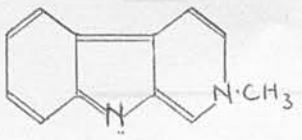
LI



LII

In the carbolinium cation, both forms carry a positive charge, and so here the completely aromatic form has predominance because it has no special disadvantage due to charge distribution relative to the other possible forms. This distribution of charge can only take place if the system connecting the charged centres is a conducting one. In other words, the necessary changes in covalency must be not merely possible, but facile, and this will be the case only with conjugated systems.

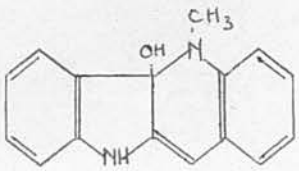
Anhydronium base formation in other carbolines and in the benzcarboline series may be similarly explained, all the considerations adduced in connection with the γ-series being relevant. It should be kept in mind, however, that when formulating the conjugated, uncharged form of β-carboline (LIII), it is necessary to postulate a long series of conjugated double bonds round the periphery of the molecule, in contrast with the simple short system of the α- and γ-series.



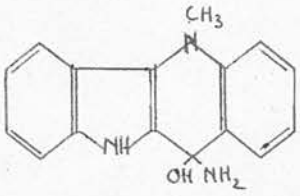
LIII

A notable exception to anhydronium base formation in this type of compound is quindoline (—)

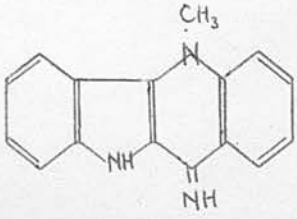
and 7-aminoquindoline, whose metho salts give a pseudo base of type (LIV), (Holt and Petrow, 1948.). The metho salt of 2-aminoquindoline gives a pseudo base of type (LV), which may be converted to the ether by crystallisation from ethanol and then dealcoholated to give the anhydronium base (LVI). The quaternary salt of 7-nitroquinindoline, however, by virtue of the activating effect of the 7-nitro grouping on the pyrrole hydrogen, readily passes into the anhydronium base 7-nitro-5-methylisoquinindoline on treatment with alkali. (Holt and Petrow, 1948.)



LIV



LV



LVI

DISCUSSION

GENERAL DISCUSSION

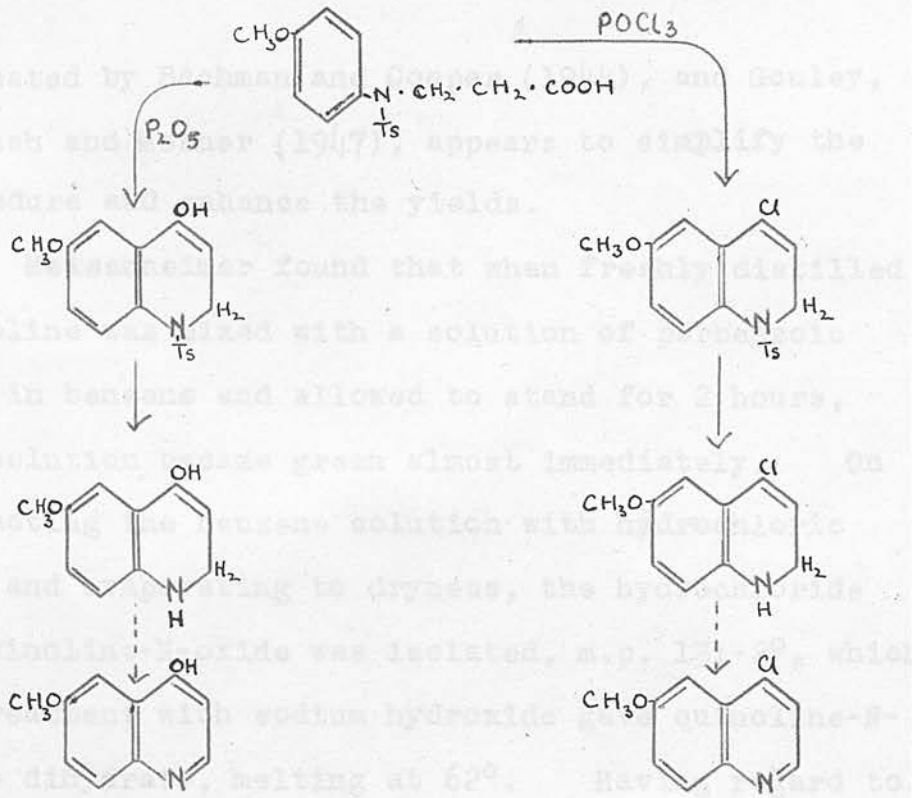
As mentioned in the previous section, one of the main objects of this research is to synthesise 2:3-benz-γ-carboline, and from it to prepare various basic derivatives.

A general procedure for the synthesis of 2:3-benz-γ-carbolines, using the Graebe-Ullmann carbazole synthesis, has been worked out by Kermack and Smith (1930). This consists of heating the appropriate 4-(benztriazolyl-1')quinoline derived from 4-o-aminophenylaminoquinoline, in boiling phosphoric acid and isolating the base from the resulting solution. The method is essentially the same as that used by Robinson and Thornley, (1924), in preparing γ-carboline from 4-chloropyridine and o-phenylenediamine, via 4-o-aminophenylaminopyridine and the triazole derivative. By an analogous series of reactions, 2:3-benz-γ-carboline has been prepared from 4-chloroquinoline and o-phenylenediamine. o-Phenylenediamine was readily obtained commercially; but 4-chloroquinoline had to be synthesised, and a considerable amount of work was carried out to determine the most suitable

method of synthesis.

An observation by Clemo and Perkin (1924;1925) that certain β-anilinopropionic acids as their N-p-toluenesulphonyl (tosyl) derivatives undergo ring closure to dihydro-4-quinolones when treated with phosphorus pentoxide, suggested the possibility that these acids might serve as a convenient source of 4-hydroxyquinoline, from which 4-chloroquinoline could readily be obtained. Clemo and Perkin also recorded the formation of 1-tosyl-3-chloro-dihydroquinolines when the anilinopropionic acid derivatives were subjected to the action of phosphorus oxychloride. Backeberg (1933), however, has shown that the product of this reaction is in actuality 1-tosyl-4-chloro-1:2-dihydroquinoline, from which a small amount of 4-chloroquinoline was obtained on oxidation.

Elderfield et al. (1946) investigating this method of preparation for 4-chloroquinolines, found that the ring closure of β-anisidinopropionic acid to the quinoline derivative led mainly to tars and intractable oils under a variety of conditions. When the free hydrogen on the nitrogen is protected by an acetyl or tosyl group, however, the β-anisidino propionic acid gave dihydroquinoline derivatives on ring closure.



Attempts to dehydrogenate these dihydroquinoline derivatives to quinolines using a variety of reagents such as bromine, palladiumised charcoal, arsenic pentoxide, lead peroxide and sulphur were uniformly unsuccessful, and doubt appears to be cast on the structures assigned to them. As this method of preparing 4-chloroquinoline in quantity did not appear to be fruitful, recourse was made to Meisenheimer's (1926) original preparation of the compound from quinoline-N-oxide.

In general, it is found that quinoline and related compounds form N-oxides fairly easily on treatment with organic peracids, and Meisenheimer, the first to develop the method, used perbenzoic acid exclusively. More modern usage of perphthalic acid

advocated by Bachman and Cooper (1944), and Gouley, Moersch and Mosher (1947), appears to simplify the procedure and enhance the yields.

Meisenheimer found that when freshly distilled quinoline was mixed with a solution of perbenzoic acid in benzene and allowed to stand for 2 hours, the solution became green almost immediately. On extracting the benzene solution with hydrochloric acid and evaporating to dryness, the hydrochloride of quinoline-N-oxide was isolated, m.p. 131-2°, which on treatment with sodium hydroxide gave quinoline-N-oxide dihydrate, melting at 62°. Having regard to the long and tedious preparation of perbenzoic acid (Org. Synth., Coll. Vol.1, 1st. Ed., p.422.), which necessitates an estimation at the end, and to the fact that some preliminary work carried out in this direction was not satisfactory, this approach was discontinued in favour of other, less laborious methods.

Hydrogen peroxide and glacial acetic acid have been used to prepare the N-oxide of pyrazine, and the di-N-oxides of o-, m- and p-phenanthroline (Linsker and Evans, 1946.), and it was thought desirable from the standpoint of ease of manipulation to employ these reagents in the preparation of quinoline-N-oxide. The method has already been tried by Bachman and Wetzel (1946) on 5-nitroquinoline, when a yield of 5-nitroquinoline-N-oxide of 30% was

recorded. The yield by the perphthalic acid method was in the neighbourhood of 67%. Renfrew (1946) found that 7-methylquinoline will yield an N-oxide on treatment with hydrogen peroxide, but paralleled Bachman's results in finding the yield to be much inferior to that obtained by the perphthalic acid method. In view of the simplicity of the method, an attempt was made to prepare quinoline-N-oxide in this way. Freshly distilled quinoline was dissolved in glacial acetic acid and hydrogen peroxide solution (100 vol.). After boiling under reflux for 2 hours, during which time there was a colour change from light yellow to deep orange, the reaction mixture was cooled to room temperature, diluted with water and neutralised with saturated potassium carbonate solution. The solution was left in the ice box for 16 hours, during which period a small precipitate formed, which was filtered, washed with water and dried. On crystallisation from benzene, the melting point could not be raised above 46°. (Meisenheimer recorded a m.p. of 61° for the quinoline-N-oxide dihydrate.) The yield was in the neighbourhood of 30%. Despite the dissimilarity of melting points, the compound appeared to be quinoline-N-oxide hydrate, since when treated with a saturated solution of picric acid in benzene, a

picrate was obtained melting at 140-4° (Meisenheimer quoted 143°.), and on treatment with phosphorus oxychloride yielded 4-chloroquinoline.

A variety of temperatures and concentrations of the reagents was employed in an attempt to increase the yield of the N-oxide, and in order to discover, if possible, the fate of the unaccounted for quinoline. When the above experiment was carried out at 50-70°, at room temperature, or at room temperature with a trace of peroxidase present to catalyse the reaction, various amounts of unchanged quinoline were isolated, indicating that the oxidation had not gone far enough. On the other hand, when the mixture was refluxed gently for more than two hours at a time, a tar was found to separate on dilution with water, indicating that the reaction had proceeded further than was desired. From this, there would appear to be two main ways of controlling the reaction, namely, (a) by adding an inhibitor to the reaction carried out at high temperature, or (b) by using an efficient catalyst at low temperatures. In connection with (b), the use of osmium tetroxide suggested itself. Milas and Sussman (1936), engaged in the preparation of tertiary alkyl peroxides and hydroperoxides, found that anhydrous solutions of hydrogen peroxide and tertiary butyl alcohol in the presence of a small amount of osmium

tetroxide, reacted readily with olefinic double bonds to give, almost invariably, a glycol. Criegee (1936) on the other hand, in preliminary results using osmium tetroxide and hydrogen peroxide in ethyl ether, obtained aldehydes as the main products of oxidation, indicating how by altering conditions, the reaction may be made to give higher or lower oxidised products.

Another interesting reaction carried out with hydrogen peroxide in tertiary butyl alcohol with osmium tetroxide as catalyst (Milas's reagent) was described by Anderson (1949). He found that when N:N-dimethyl-p-aminoazobenzene is treated with the reagents at 37° for 12 hours, a mixture of products is formed. This consists mainly of N-methyl-p-aminoazobenzene, p-aminoazobenzene and p-nitroazobenzene. Removal of alkyl groups from aromatic tertiary amines is not uncommon in <u>in vivo</u> reactions, but little is known of the reaction mechanism. The above provides an example of oxidative demethylation of an aromatic tertiary amine effected by hydrogen peroxide.

To investigate the reaction with regard to the oxidation of quinoline to quinoline-N-oxide, an experiment was carried out along the lines developed by Milas. Freshly distilled butyl alcohol (tertiary) was dried over calcium sulphate for 48 hours,

and subjected to reduced pressure for 3 hours to remove any trace of isobutylene. (Otherwise, osmium tetroxide is readily reduced to an insoluble, black, colloidal oxide which is a very active catalyst for the decomposition of hydrogen peroxide.) The prepared tertiary butyl alcohol was added to 30% hydrogen peroxide, and the solution was treated with small amounts of anhydrous sodium sulphate, whereby two layers separated. The alcohol layer, which contained most of the hydrogen peroxide, was removed and dried with anhydrous calcium sulphate. A solution of approximately 6.3% hydrogen peroxide in tertiary butyl alcohol was obtained.

Two experiments were set up, one with and the other without osmium tetroxide as catalyst.

1. The hydrogen peroxide - butyl alcohol solution and quinoline were shaken together, cooled in the ice box for 2 hours, and then left at room temperature for 18 hours. No change was detectable in the solution, which was evaporated to a small volume under reduced pressure at 50°, and divided into three portions a, b and c.

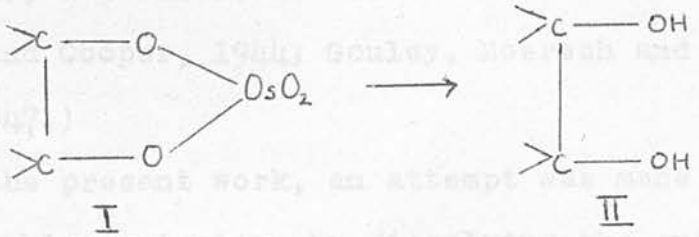
a, was poured into water, and as no crystalline material resulted, was converted into the picrate, m.p. 198-200°.

b, was poured into hydrochloric acid, no solid material resulting.

c, was dissolved in ethanol and treated with a saturated alcoholic solution of picric acid; a picrate separated, melting at 195-200°. When the picrates from a and c were crystallised from ethanol, they melted at 203-5°, and were shown to be quinoline picrate,(m.p. 205°) by mixed melting point. This indicates that no reaction had taken place.

2. The above reaction was repeated in the presence of a small amount of osmium tetroxide. The residue, after removal of the solvent, was taken up in a water, b hydrochloric acid, and c alcohol, as before. A, gave a picrate melting at 186-8°, b, yielded no solid material, and c, gave a picrate melting at 188-90°. On crystallisation from ethanol, the melting points of the picrates could not be raised above 190°, which suggested the presence of quinoline picrate contaminated with a small amount of quinoline-N-oxide picrate. (Meisenheimer, 143°.) On the other hand, the sharpness of the melting point suggested that a pure compound was present, and it is not unlikely that the osmic acid has reacted with an ethylenic double bond in the quinoline with the formation of an osmic ester (I), which has been converted into a cis-diol (II) These experiments suggested that the oxidation of quinoline to quinoline-N-oxide by hydrogen peroxide and osmium tetroxide did not proceed with any

facility, and so the exploration of the route was abandoned.



I II

The treatment of N-oxides with sulphuryl chloride was first investigated by Meisenheimer (1926), who obtained a good yield of 4-chloroquinoline by refluxing the quinoline-N-oxide and sulphuryl chloride together for 5 hours. Bobranski (1938), repeating Meisenheimer's experiments, found that 2-chloroquinoline was also formed in the reaction, but that it had not been detected by Meisenheimer since he isolated his product as a picrate from ethanol. (2-chloroquinoline forms a picrate which is very soluble in ethanol, and is not readily isolated from this solvent.) Bobranski found that 4-chloroquinoline is formed in about 60% yield, and 2-chloroquinoline in about 38%; a little tetrachloroquinoline was also obtained from the mother liquors.

The ratio of isomers produced in such a reaction has been found to depend on the nature of the substituents in other positions in the ring, and to be little influenced by changes in the reaction conditions. (Bachman and Cooper, 1944.) In

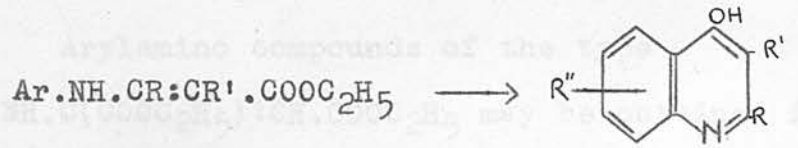
certain cases, for example, during the treatment of 5- and 6-nitroquinoline-N-oxides with phosphorus oxychloride, a 3-chloro isomer was also isolated. (Bachman and Cooper, 1944; Gouley, Moersch and Mosher, 1947.)

In the present work, an attempt was made to prepare 4-chloroquinoline by dissolving the quinoline-N-oxide dihydrate (m.p. 42°, see p. 43) in phosphorus oxychloride, and refluxing the mixture for 30 minutes. The clear solution was allowed to cool, and when cold was poured on to ice. The resulting solution on treatment with ammonium hydroxide yielded an oil, which eventually solidified to give a material, m.p. 25-30°. Attempts to prepare a picrate in alcoholic solution were unsuccessful, only a yellow, gummy material which did not crystallise being obtained. The recorded melting point of 4-chloroquinoline is quoted as 31° by Meisenheimer, and that of 2-chloroquinoline as 37-8°. It would seem, then, that a small amount of 4-chloroquinoline was produced during the reaction, though as a whole the experiment was unsatisfactory.

It soon became obvious that this line of research was not profitable as a method of preparing 4-chloroquinoline, though interesting results may have arisen had it been further extended. At the

present juncture, it was decided to investigate other methods of synthesis, and in particular those which the American workers have been using in their preparation of intermediates for the synthesis of drugs of the 4-aminoquinoline type.

Nearly all these methods involve the high temperature cyclisation of the type of compound which may be represented by (III); 4-hydroxyquinolines of the general formula (IV) then result.

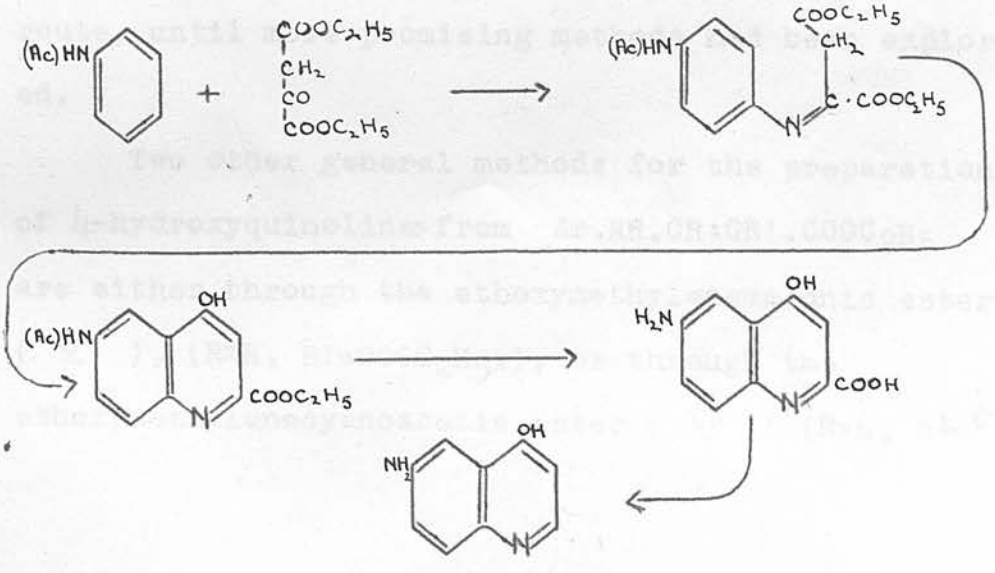


III IV

The simplest and most direct method of preparing 4-chloroquinolines in this way, would be the cyclisation of $Ar.NH.CH:CH.COOC_2H_5$ (R=R'=H in III) and the conversion of the resulting 4-hydroxyquinoline to the 4-chloro derivative by treatment with phosphorus oxychloride. Although earlier workers encountered difficulty in cyclising anilinoacrylates of this type, (Rubtsov, 1938.) Price, Leonard and Reitsema (1946) found that methyl and ethyl m-chloroanilinoacrylates cyclise fairly readily in a large volume of diphenyl/diphenyl ether mixture, to give 40% of 7-chloro and 10% of 5-chloro-4-hydroxyquinoline. When a small volume of the diluent was used

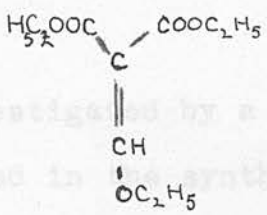
bis-(m-chlorophenyl)urea was formed. Ethyl β-anilinoacrylate was cyclised in 44% yield to 4-hydroxyquinoline by the same method. The authors prepared the acrylates by the action of ethyl and methyl formylacetates, in the form of their sodio derivatives, on m-chloroaniline and aniline in acetic acid. The yield from the condensations was poor, in the neighbourhood of 25% , and the method did not appear suitable for the large scale preparation of intermediate hydroxyquinolines.

Arylamino compounds of the type $Ar.NH.C(COOC_2H_5):CH.COOC_2H_5$ may be obtained from arylamines and ethyl oxaloacetate. These, after cyclisation, hydrolysis and decarboxylation, yield quinoline derivatives, and the method has been used successfully by Kermack and Weatherhead (1940) in the synthesis of 4-hydroxy-6-aminoquinoline, as shown below.

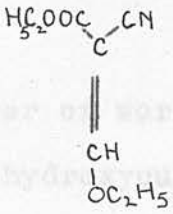


It was later used by Surrey and Hammer (1946) in the preparation of 7-substituted 4-hydroxyquinolines. Riegel et al.,(1946b.), in a critical investigation of the method, found that cyclisation of the anilino compound by means of refluxing diphenyl ether was in general satisfactory, and that decarboxylation of the acid after saponification of the ~~acid~~ ester, could be effected by heating in the same solvent. These two steps, however, were found to require conditions which varied widely, depending on the substituents in the carbocyclic ring. In the case of p-anisidine, for example, mineral oil had to be employed as diluent, because the product was too soluble in diphenyl ether. The authors prepared 4-hydroxyquinoline and 4-hydroxy-6-methoxyquinoline by the method. Nevertheless, as ethyl sodiooxaloacetate - from which ethyl oxaloacetate is obtained - is not readily available in large quantities, it was decided to postpone an investigation of this route, until more promising methods had been explored.

Two other general methods for the preparation of 4-hydroxyquinolines from $Ar.NH.CR{:}CR'.COOC_2H_5$ are either through ~~the~~ ethoxymethylenemalonic ester (V), (R=H, $R'=COOC_2H_5$.), or through ~~the~~ ethoxymethylenecyanoacetic ester (VI) (R=H, R= CN



V



VI

It was found by Price, Leonard and Herbranson (1946) that the preparation of the ethoxymethylene-cyanoacetic ester offered no particular advantage over the synthesis of diethylethoxymethylene malonate, and that the arylaminocyanoacrylate required much higher dilution for cyclisation than did the corresponding arylaminocarbethoxyacrylate.

Snyder and Jones (1946) simplified the method of preparation of the arylaminocyanoacrylate considerably, by showing that ethyl cyanoacetate, an aromatic amine and ethyl orthoformate when heated together give a good yield of α-cyano-β-anilinoacrylate, according to either of the equations

1. $2ArNH_2 + HC(OC_2H_5)_3 \longrightarrow ArN{:}CH.NHAr$

2. $ArN{:}CH.NHAr + CN.CH_2.COOC_2H_5 \longrightarrow ArNH.CH{:}\underset{\displaystyle COOC_2H_5}{\underset{|}{C}}.CN$

or

1. $CN.CH_2.COOC_2H_5 + CH(OC_2H_5)_3 \longrightarrow C_2H_5OCH{:}\underset{\displaystyle CN}{\underset{|}{C}}.COOC_2H_5$

2. $C_2H_5OCH{:}\underset{\displaystyle CN}{\underset{|}{C}}.COOC_2H_5 + ArNH_2 \longrightarrow ArNH.CH{:}\underset{\displaystyle COOC_2H_5}{\underset{|}{C}}.CN$

The use of diethylethoxymethylene malonate has

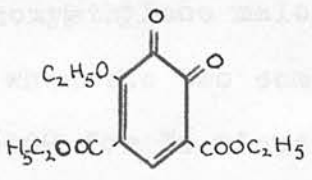
been investigated by a large number of workers interested in the synthesis of 4-hydroxyquinolines; Price and Roberts reported the formation of substituted anilinomethylenemalonic esters from substituted anilines and the ethoxymethylenemalonate to proceed easily and almost quantitatively, a conclusion supported by other workers. This method therefore appeared preferable to the arylaminocyanoacrylate route, and suitable for the preparation of 4-chloro-, 6-methoxy-4-chloro-, and 4:6-dichloroquinoline desired by us, and was consequently chosen for study in the present research.

Diethylethoxymethylene malonate was first prepared by Claisen (1897), who obtained it in 40% yield by heating together diethyl malonate, ethyl orthoformate, acetic anhydride and zinc chloride at 110-12° for 11-12 hours. The mechanism of the reaction has since been investigated by Fuson, Parham and Reed (1946), who found diethyldiethoxymethyl malonate to be the precursor of diethylethoxymethylene malonate in the reaction. In view of this, they advocated prolonged heating of the mixture at a high temperature (145-55°) without the removal of the zinc salts, in order to facilitate the decomposition of the diethyldiethoxymethyl malonate and increase the yield of the desired ester. Results verified this expectation, and the authors obtained a 63% yield of

diethylethoxymethylene malonate. In direct contrast, a note was recently published by Duffin and Kendall (1948) indicating that prolonged heating lowered the yield of product, and that provided the operations were carried out rapidly, yields higher than those claimed by Claisen were obtained (ranging from 40 to 48%).

In the present research, a method kindly supplied by I.C.I.Ltd. was followed. This entailed heating a mixture of diethyl malonate, ethyl orthoformate and acetic anhydride, in presence of zinc chloride, for 10 hours, and in our hands gave an average yield of 65% of theory. It will be seen that this considerably exceeds that obtained by Duffin and Kendall, and is almost identical with the yield quoted by Fuson, Parham and Reed.

In all the preparations of diethylethoxymethylene malonate carried out, a brown residue remained which crystallised on cooling. The compound melted at 94-6°, and was assumed to be ethyl ethoxy-α-pyrone dicarboxylate by Claisen, who also isolated it. This has been verified by Fuson et al., who showed the compound to be 3:5-dicarbethoxy-6-ethoxy-α-pyrone (VII).

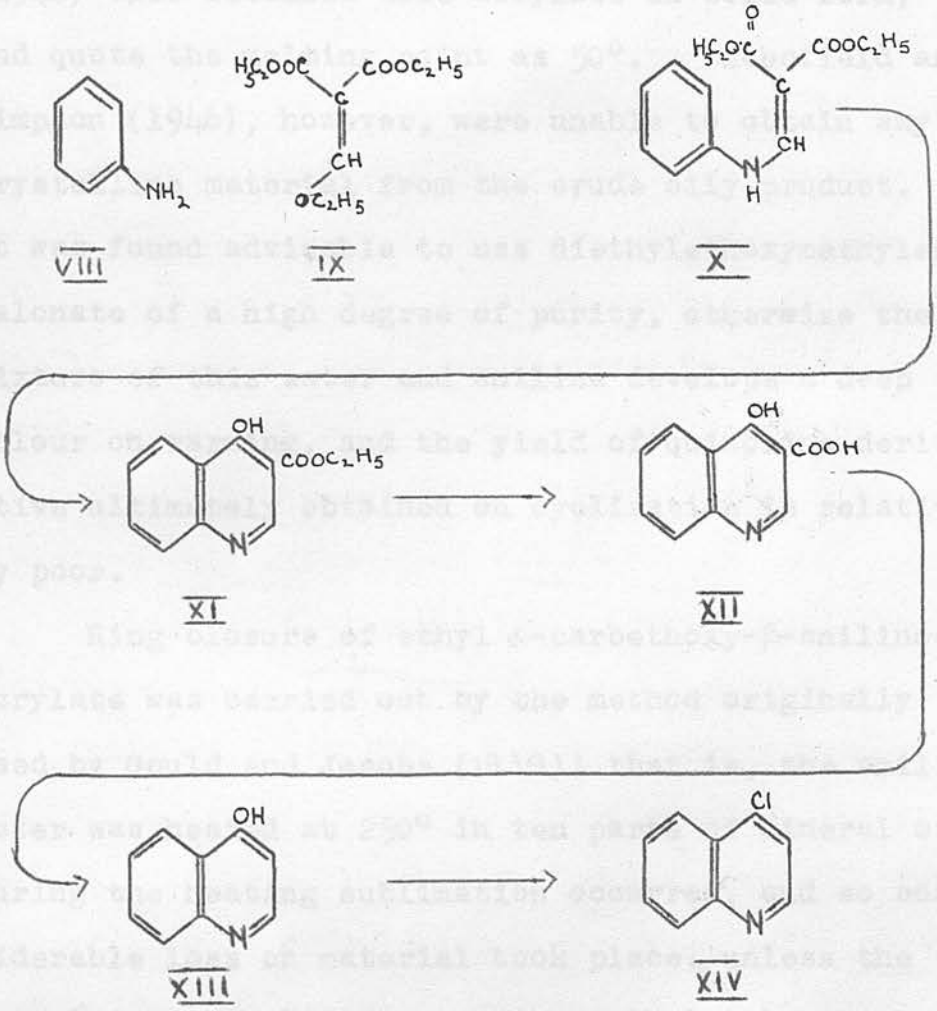


VII

THE SYNTHESIS OF 2:3-BENZ-γ-CARBOLINE.

(a.) The preparation of 4-chloroquinoline.

4-Chloroquinoline was prepared according to formulae (VIII) to (XIV).



VIII IX X XI XII XIII XIV

Diethylethoxymethylene malonate condensed easily with aniline when the two compounds were heated together at 100° for 30 minutes, the ethanol formed during the course of the reaction being

removed under reduced pressure. The product, a brown oil, solidified on standing to give a buff-coloured solid, which when crystallised from light petroleum (40/60°) yielded large, clear plates, (X), m.p. 46-8°. Claisen (1897) and Duffin and Kendall (1948) also obtained this acrylate in solid form, and quote the melting point as 50°. Schofield and Simpson (1946), however, were unable to obtain any crystalline material from the crude oily product. It was found advisable to use diethylethoxymethylene-malonate of a high degree of purity, otherwise the mixture of this ester and aniline develops a deep colour on warming, and the yield of quinoline derivative ultimately obtained on cyclisation is relatively poor.

Ring closure of ethyl α-carbethoxy-β-anilino-acrylate was carried out by the method originally used by Gould and Jacobs (1939); that is, the anilino ester was heated at 250° in ten parts of mineral oil. During the heating sublimation occurred, and so considerable loss of material took place, unless the containing vessel was covered as completely as possible. Ethyl 4-hydroxyquinoline-3-carboxylate(XI)when washed free of mineral oil by light petroleum and crystallised from ethanol, melted at 273-4°. (Schofield and Simpson, 275-6°.)

With recrystallised anilino esters, the ring closure went smoothly, and in one sense only, but attempts at cyclisation before purification gave low yields of dark products, and it was found that the combined mineral oil filtrate and light petroleum extract deposited a white solid of melting point 110-2° on standing. This compound, when crystallised from light petroleum (60/80°) gave needles, of melting point 114-6°. The product was insoluble in hot sodium carbonate, cold sodium hydroxide and cold 2N hydrochloric acid. It was clearly identical with the compound similarly isolated by Schofield and Simpson (1946), m.p. 118° and empirical formula $C_{18}H_{18}O_3N_2$. The nature of the product will be discussed later. (see page 61 .)

Ethyl 4-hydroxyquinoline-3-carboxylate, when hydrolysed by heating with 5% aqueous sodium hydroxide, followed by acidification with acetic acid, gave the free carboxylic acid in almost quantitative yield. Price and Roberts (1946) favoured boiling 18% hydrochloric acid as hydrolysing agent, from which the free carboxylic acid separated on cooling. In this method, there is the possibility of hydrochlorides forming, and in the present thesis, alkaline hydrolysis was used throughout. 4-Hydroxyquinoline-3-carboxylic acid when crystallised from nitrobenzene was found to melt at 268-70°, with effervescence, in

agreement with Schofield and Simpson.

It was discovered that if unpurified ethyl 4-hydroxyquinoline-3-carboxylate, prepared from crude ethyl ∝-carbethoxy-β-anilinoacrylate is used in the hydrolysis, then the 5% aqueous sodium hydroxide solution deposits a sodium salt on cooling, (N.B. The sodium salt of 4-hydroxyquinoline-3-carboxylic acid is very soluble in water.) Furthermore, if the hot, 5% sodium hydroxide solution is acidified with dilute acetic acid, the product is found to be only partially soluble in sodium carbonate; and if dilute alkali is used to extract the 4-hydroxyquinoline-3-carboxylic acid from the product, a residue is left having a melting point of 314-6°. It is insoluble in aqueous sodium carbonate or hydrochloric acid, but is soluble in hot aqueous sodium hydroxide , from which a colourless sodium salt separates on cooling. The substance was crystallised from glacial acetic acid, giving clear plates melting at 318-20°. The compound is evidently identical with the substance of melting point 318°, and empirical formula $C_{16}H_{12}O_2N_2$ or $C_{15}H_{12}O_3N_2$ obtained by Schofield and Simpson when the mother liquors from the crystallisation of crude ethyl 4-hydroxyquinoline-3-carboxylate were evaporated to dryness. The constitution of this compound will also be discussed on page 61.

There are three recognised methods for decarboxylating carboxylic acids; namely, (a.) direct heating, (b.) heating in a neutral solvent, and (c.) heating in a basic solvent in presence of a catalyst. Method (a.) is the simplest, as it only involves heating a small quantity of the dry acid at its melting point until the evolution of carbon dioxide ceases. For larger scale work, methods (b.) and (c.) are more economical. The combination of solvent and catalyst (c.) was found to give very satisfactory results, as described by Kermack and Weatherhead (Weatherhead, Thesis, Edinburgh, 1939.) in the decomposition of 6-acetamido-4-hydroxyquinoline-2-carboxylic acid, and by Douglas and Kermack (1948) in the decarboxylation of 4-hydroxy-3-carboxy-p-phenanthroline. In these cases, quinoline was used as solvent, and copper-bronze or copper-barium chromite as catalyst. Some difficulty has been encountered in decarboxylating certain acids, and this is particularly true of those acids containing a nitro group in the 8-position. However, it was discovered by Baker *et al.* (1946) that pyrolysis of the silver salts of the acids in diphenyl gave reasonable yields, which were reproducible in large scale runs.

4-Hydroxyquinoline-3-carboxylic acid was decarboxylated to 4-hydroxyquinoline in the present

instance, either by heating the acid in a test tube over a free flame, or by adding the acid in small portions to hot mineral oil, and heating at 270-300° until the acid dissolved. In our opinion, both methods were wasteful, as the decarboxylated product sublimed and evaporated in the form of white fumes. A more successful way of decarboxylating the acids was used in the methoxy series, and will be described later.

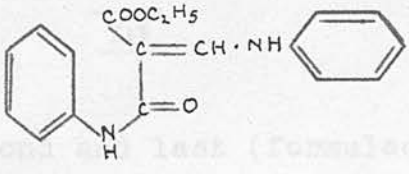
4-Hydroxyquinoline was converted into 4-chloroquinoline by refluxing gently with phosphorus oxychloride. The product was readily obtained pure, and in good yield.

(b.) <u>The constitution of the by-products isolated during the synthesis of 4-chloroquinoline.</u>

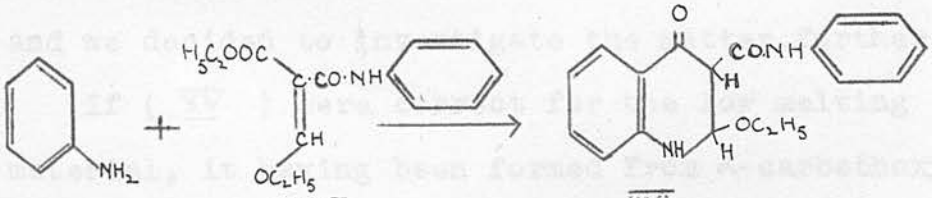
As mentioned earlier (p. 58), a compound of melting point 118°, and empirical formula $C_{18}H_{18}O_3N_2$ crystallised from the mineral oil - light petroleum filtrate, from which ethyl 4-hydroxyquinoline-3-carboxylate had been previously separated. In addition, it was found that when crude ethyl 4-hydroxyquinoline-3-carboxylate was hydrolysed by 5% sodium hydroxide, a by-product , m.p. 318° and empirical formula $C_{16}H_{12}O_2N_2$ or $C_{15}H_{12}O_2N_2$ was obtained (page 59).

The nature of these products will now be discussed.

Schofield and Simpson in their paper of 1946 noted that the empirical formula of these substances indicated that two molecules of arylamine are involved, and suggested either (XV) or (XVI) as possible structures for the lower melting material ($C_{18}H_{18}O_3N_2$), (XVII) being considered as a possible intermediate in the latter case.



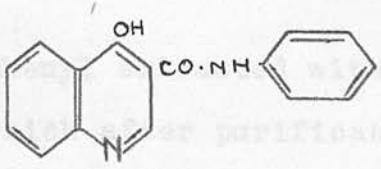
XV



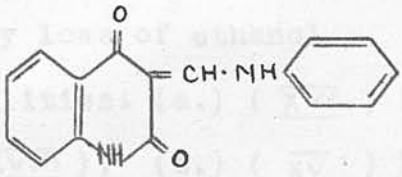
XVII XVI

That either (XV) or (XVI) should survive the conditions of the reaction without loss of ethanol is rather surprising, and no final decision was reached as to the structure of the compound.

Schofield and Simpson suggested the constitution of the higher melting compound ($C_{16}H_{12}O_2N_2$) to be either (XVIII) formed from (XVI) by loss of ethanol, or (XIX) formed from (XV) by loss of ethanol.



XVIII

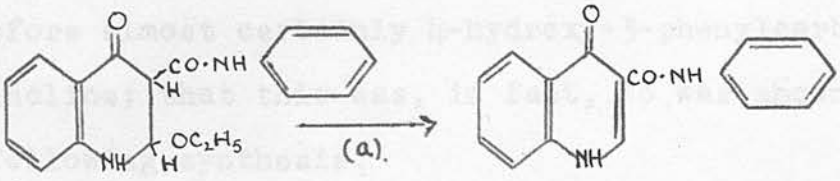


XIX

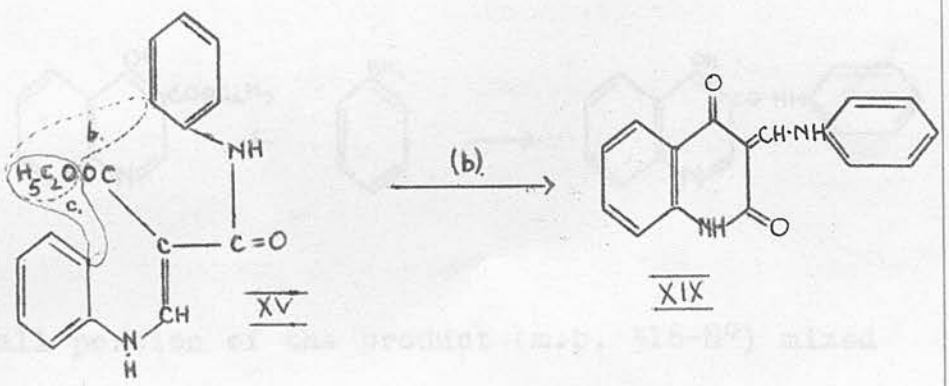
The authors' second and last (formulae XVI and XIX) representations of the two by-products of melting points 118° and 318° respectively, isolated in these experiments, appeared to us to be rather unusual, and we decided to investigate the matter further.

If (XV) were correct for the low melting material, it having been formed from α-carbethoxy-β-anilinoacrylate and another molecule of aniline, of by the mechanism suggested by Schofield and Simpson, then this compound, if it were heated in liquid paraffin at 250°, might be expected to cyclise to give a compound of structure (XVIII), rather than (XIX) as suggested by Schofield and Simpson. In order to test the validity of the suggestion, some of the lower melting product was heated in boiling diphenyl for 30 minutes. The solution was

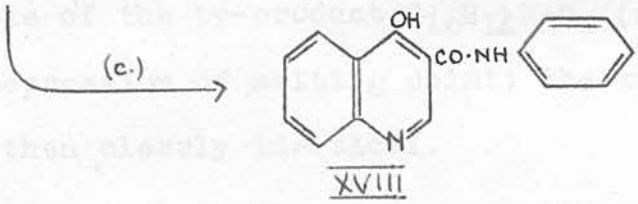
cooled and the diphenyl extracted with ether to leave a solid residue, which after purification melted at 318°. The compound showed no depression in melting point when mixed with a sample of the high melting by-product (m.p. 318°). This proves that the lower melting material definitely passes into the higher melting compound by loss of ethanol. There are thus three possibilities: (a.) (XVI) has lost ethanol to give (XVIII); (b.) (XV) has cyclised to give (XIX), or (c.) (XV) has cyclised the other way to give (XVIII).



XVI XVIII



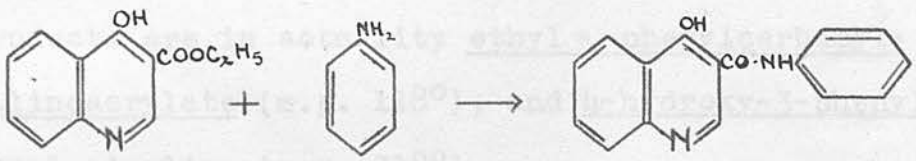
XV XIX



XVIII

Of these possibilities, the third explanation seemed to us the most likely, and this was confirmed when it was found that the high melting material could be hydrolysed by acid to give 4-hydroxyquinoline-3-carboxylic acid, and a diazotisable amine. Thus when a portion of the solid was refluxed with 5% sulphuric acid, the solution was found to give a positive diazo test, indicating the presence of a primary aromatic amine, and to deposit a solid of melting point 265-7° on cooling. The solid was shown to be 4-hydroxyquinoline-3-carboxylic acid by mixed melting point. The original compound was therefore almost certainly 4-hydroxy-3-phenylcarbamylquinoline; that this was, in fact, so, was shown by the following synthesis.

4-Hydroxy-3-phenylcarbamylquinoline was prepared by refluxing ethyl 4-hydroxyquinoline-3-carboxylate with aniline as shown.



A small portion of the product (m.p. 316-8°) mixed with a sample of the by-product $C_{16}H_{12}N_2O_2$ (m.p. 318°) showed no depression of melting point; the two compounds are then clearly identical.

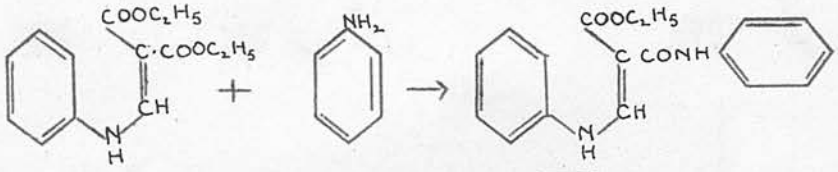
As already indicated, the lower melting material

($C_{18}H_{18}O_3N_2$) can pass into the higher melting material ($C_{16}H_{12}O_2N_2$) on pyrolysis with loss of ethanol. Since the $C_{16}H_{12}O_2N_2$ material has been just proved to be 4-hydroxy-3-phenylcarbamylquinoline, two possibilities of structure for the low melting substance remain, namely (XV) or (XVI). That the compound has formula (XV) has been shown by our synthesis of it in the following manner.

Ethyl α-phenylcarbamyl-β-anilinoacrylate was prepared by heating ethyl α-carbethoxy-β-anilinoacrylate with an equimolecular amount of aniline for one hour at 100°. (formulae XX to XXI.) The product, obtained in good yield, melted at 116-8° and showed no depression in melting point when mixed with some of the by-product $C_{18}H_{18}O_3N_2$, indicating that the two compounds are identical. That (XVI) could have been formed in this reaction is highly unlikely, as this would involve loss and re-addition of ethanol. From this, it is clear that the two by-products are in actuality ethyl α-phenylcarbamyl-β-anilinoacrylate (m.p. 118°), and 4-hydroxy-3-phenylcarbamylquinoline (m.p. 318°).

The formation of these by-products only occurs if impure diethyl ethoxymethylenemalonate or excess aniline is used, no difficulties being experienced when pure anilinoacrylate was cyclised. It would appear that Schofield and Simpson's trouble was

due largely to impurities in their starting material; This would also account for the fact that in their hands ∝-carbethoxy-β-anilinoacrylate would not cyrstallise.



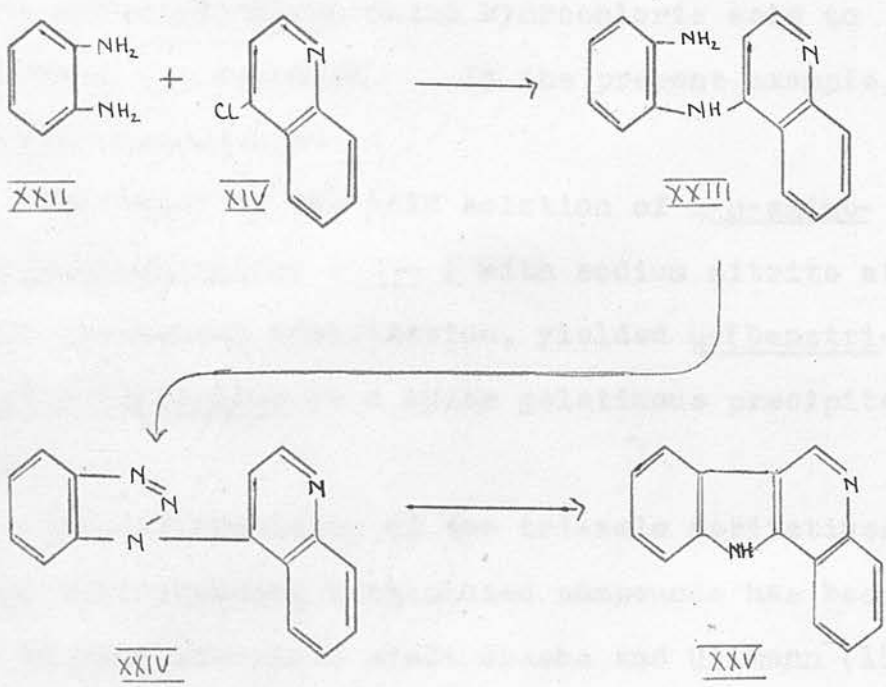
XX XXI

It may be significant to note that Surrey and Hammer (1946) found that the yields of 4-hydroxy- 2-carbethoxyquinolines in the closely analogous syntheses from arylamines and oxaloacetic ester, are diminished if the primary adduct contains free amine. Though they found it advantageous to use excess of the aniline to obtain better yields of the anilino ester, practically all the unreacted aniline had to be removed before the next step was commenced; otherwise the process of cyclisation was interfered with.

(c.) The preparation of 2:3-benz-γ-carboline from 4-chloroquinoline.

In order to apply the Graebe-Ullmann synthesis for the preparation of 2:3-benz-γ-carboline, formulae

(XXII) to (XXV), it was first necessary to obtain the appropriate 4-o-aminophenylaminoquinoline (XXIII).



This was prepared without difficulty from o-phenylenediamine (XXII) and 4-chloroquinoline (XIV) by heating the two reactants together at 140°, under a pressure of 30-20 mm.; after the manner of Kermack and Smith (1930). The reaction was vigorous, and took place after a lag period of some 10-20 minutes, depending on the pressure. Heralded by one or two bubbles rising to the surface of the viscous solution, the whole mixture frothed up and set to a hard, porous solid. The free base was obtained from the solution of the product in dilute hydrochloric acid by basification, and was isolated in good yield.

Holt and Petrow (1948) in an analogous preparation, found it advantageous to add a slight excess of o-phenylenediamine, a trace of copper powder and one or two drops of concentrated hydrochloric acid to facilitate the reaction. In the present example, this was unnecessary.

Treatment of the acid solution of 4-o-aminophenylaminoquinoline (XXIII) with sodium nitrite at 5° and subsequent basification, yielded 4-(benztriazolyl-1')quinoline as a white gelatinous precipitate. (XXIV).

The decomposition of ~~the~~ triazole derivatives to the corresponding ring-closed compounds has been used in many reactions since Graebe and Ullmann (1896) prepared carbazole (XXVII) from the dry distillation of phenylbenztriazole (XXVI).

XXVI XXVII

Delétra and Ullmann (1904) found that this decomposition also occurred on heating certain substituted aryl benztriazoles with the formation of nitrogen and carbazole derivatives. Lawson and Perkin (1924) in an attempt to modify the conditions, found that 1-α-pyridylbenztriazole (XXVIII) may be distilled

in a vacuum without decomposition. It was thus much more stable than the purely benzenoid analogues. Ultimately, they found that its decomposition with the formation of α-carboline (XXIX) could be accomplished by strongly heating it with fused fused zinc chloride.

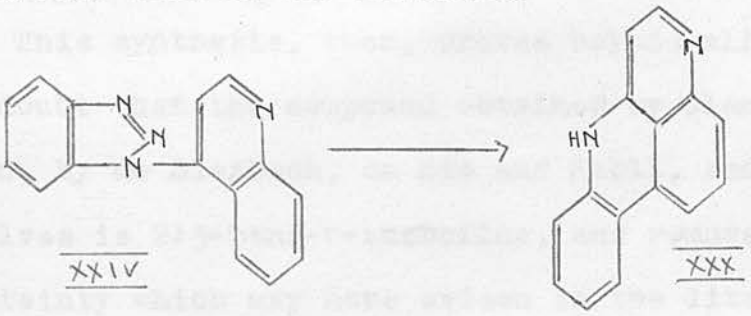
XXVIII XXIX

1-α-quinolylbenztriazole when strongly heated in small quantities at ordinary pressures, decomposed into 2:3-benz-α-carboline; the relative facility of the reaction may be due to its higher boiling point. Robinson and Thornley (1924) also experienced considerable difficulty in effecting the decomposition of triazoles, and in particular that of 1-γ-pyridylbenztriazole. This is a far stronger base than 1-α-pyridylbenztriazole prepared by Lawson, Perkin and Robinson, but like the latter, it may be distilled in a vacuum without decomposition. Robinson and Thornley, however, observed that the change proceeded smoothly when the compound was heated in boiling syrupy phosphoric acid. Holt and Petrow (1948) have since shown that pyrolytic decomposition of triazoles failed to occur in neutral or basic media

such as nitrobenzene, liquid paraffin or quinoline at their boiling points, but the authors confirmed the smooth decomposition which takes place in syrupy phosphoric acid at 170°.

In our hands, too, the acidic medium proved effective, and we decomposed 4-(benztriazolyl-1')-quinoline (XXIV) into 2:3-benz-γ-carboline (XXV), by heating it in syrupy phosphoric acid until the evolution of nitrogen ceased. The base was isolated from the solution by dilution with water and basification with ammonium hydroxide. Crude 2:3-benz-γ-carboline thus obtained showed a marked violet fluorescence in concentrated sulphuric acid, which suggested that the compound might differ from that obtained by Clemo and Perkin (see page 23), who reported that the solution of their base in sulphuric acid was devoid of fluorescence. However, when the compound prepared from the triazole was subsequently crystallised from methanol, the fluorescence in concentrated sulphuric acid became less and less marked, until finally, when an analytically pure specimen was produced, its solution showed no fluorescence whatsoever. We were unable to isolate any fluorescing material from the mother liquors of the base, and the by-product was presumably present in very small quantities.

Although there is little doubt that the Graebe-Ullmann method just applied does in fact lead to compounds of type (XXV), this synthesis is not entirely without an element of ambiguity, for the theoretical objection might be raised that a base possessing structure (XXX) could have arisen from the cyclisation of the triazole.



XXIV XXX

The method used, however, was exactly analogous to that used in the synthesis of 5-methyl-2:3-benz-γ-carboline, 15-methoxy-5-methyl-2:3-benz-γ-carboline and 1:5-dimethyl-2:3-benz-γ-carboline, the structures of which have been conclusively proved to be benz-γ-carboline derivatives (Kermack and Smith, 1930.). In addition, the general properties of the bases, e.g. solubilities and fluorescences, resemble the properties of compounds whose 2:3-benz-γ-carboline structure has been proved. (ibid.)

2:3-Benz-γ-carboline prepared unambiguously in this way melted with sublimation at 342°, as compared with the melting point of 332° recorded by de Diesbach, de Bie and Rubli (see page 27). Clemo and Perkin quoted the compound as melting with sublimation

above 320°. In all other respects, the properties of the base conform to those of the compounds prepared by Clemo and Perkin and by de Diesbach. It crystallised in prisms from methanol, in which solvent it showed a reddish-blue fluorescence, (cf. (Clemo and Perkin.), and formed a crystalline hydrochloride and nitrate.

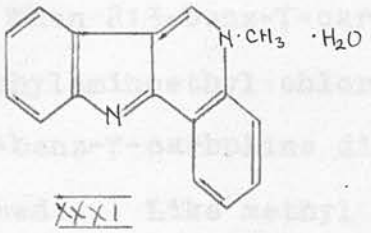
This synthesis, then, proves beyond all reasonable doubt that the compound obtained by Clemo and Perkin, by de Diesbach, de Bie and Rubli, and by ourselves is 2:3-benz-γ-carboline, and removes any uncertainty which may have arisen in the literature.

(d.) The synthesis of 2:3-benz-γ-carboline derivatives carrying a group in the 1- and 4-positions.

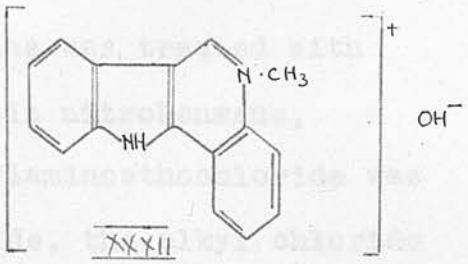
2:3-Benz-γ-carboline when warmed with methyl iodide in nitrobenzene formed a methiodide, which separated from the solution in long feathery needles. These crystals, when first isolated, were a clear white colour. On standing and drying in the air, they soon developed a pink hue which rapidly turned to a deep red and finally to black. If the crystals were washed with sodium thiosulplate, or if they were recrystallised from methanol containing a drop

of sodium thiosulphate, the colour was immediately discharged, indicating the presence of a trace of free iodine, which was forming a coloured complex ~~complex~~ with the crystals. This was confirmed when a minute amount of iodine, dissolved in ethanol, was added to the ethanolic solution of the methiodide; a dark red colour immediately developed, which deepened to black on standing. The property of developing a colour in the presence of iodine was first observed in basic compounds by Kermack, Smith and Spragg (Proc. Roy.Soc.,(Ed.)) . The compounds examined were 3:4:6:7-dibenzacridine, its methosulphate and certain 4-anilinoquinolines, all of which gave a red or blue colour with iodine at great dilution.

On adding dilute ammonium hydroxide to an aqueous solution of 2:3-benz-γ-carboline methiodide, a yellow precipitate of 4-methyl-2:3-benz-γ-isocarboline pesulted, which crystallised from benzene in clear, bright yellow prisms. On drying in a vacuum desiccator, the crystals changed to a yellow opaque powder, indicating that a solvent of crystallisation was being lost; this when analysed gave figures in agreement with the monohydrate of the expected base (XXXI), thus raising the possibility that the compound might be the carbolinium hydroxide (XXXII).



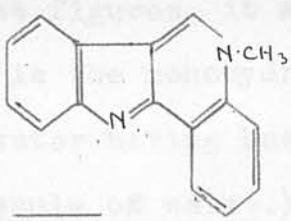
XXXI



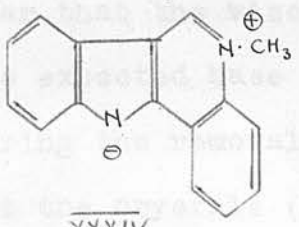
XXXII

On drying over P_2O_5 at 80° for 4 hours, however, water was lost and the resulting material analysed in agreement with the anhydrous base. A similar occurrence was observed by Robinson and Thornley (1924.), who when isolating 5-methyl-δ-isocarboline, found that analysis indicated a content of water not corresponding to any simple molecular ratio. To dehydrate it completely, the product had to be sublimed in a high vacuum at 138°, after which treatment the anhydrous material resulted.

4-Methyl-2:3-benz-γ-isocarboline is a typical anhydronium base. As mentioned in the chemical section of the introduction, the constitution of all such substances are not to be expressed by either formulae of the type (XXXIII) or (XXXIV), but by an intermediate form, in fact by a resonance hybrid.

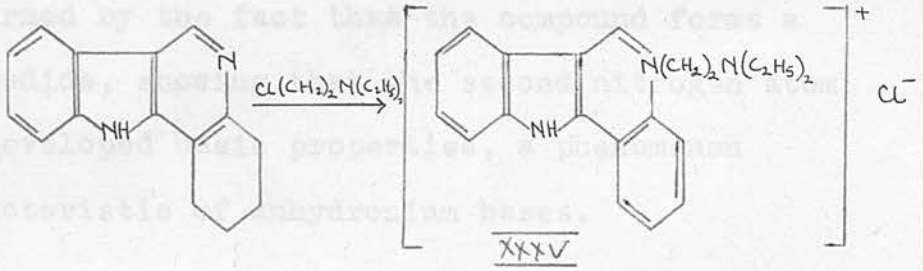


XXXIII



XXXIV

When 2:3-benz-γ-carboline was treated with diethylaminoethyl chloride in nitrobenzene, 2:3-benz-γ-carboline diethylaminoethochloride was formed. Like methyl iodide, the alkyl chloride might be expected to attach itself to the tertiary nitrogen, and this is confirmed in that a bright yellow crystalline precipitate resulted - the anhydronium ~~free~~ base - when an aqueous solution of 2:3-benz-γ-carboline diethylaminoethochloride (XXXV) was rendered alkaline with ammonium hydroxide.

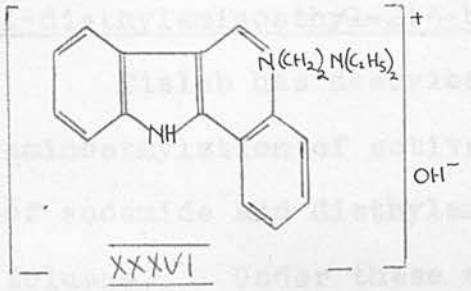


XXXV

The crystalline compound melted at 84-6°, but on being dried in a vacuum desiccator over calcium chloride turned into a highly viscous liquid. When an analytically pure specimen of the crystals were dried over P_2O_5 at 80° under vacuum, the loss in weight was 5.07%. The resulting viscous liquid then analysed for $C_{21}H_{23}N_3.1\frac{1}{2}H_2O$. From these figures, it would appear that the viscous liquid is the monohydrate of the expected base (a trace of water having been left during the removal of one molecule of water.), and that the crystals (m.p.

84-6°.) represent the dihydrate. The calculated figure for the loss of one molecule of water from the dihydrate to the monohydrate is 5.09%.

Since the dried diethylaminoethyl-2:3-benz-γ-carboline contains a molecule of water, it may clearly have been either the carbolinium hydroxide (XXXVI), or the monohydrate of the anhydronium base, 4-diethylaminoethyl-2:3-benz-γ-isocarboline (XXXVII). The compound is soluble in benzene and light petroleum, suggesting that it is the anhydronium base, rather than the carbolinium hydroxide. This is confirmed by the fact that the compound forms a methiodide, showing that the second nitrogen atom has developed basic properties, a phenomenon characteristic of anhydronium bases.



XXXVI

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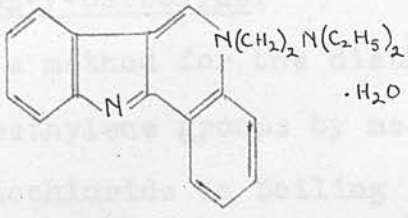
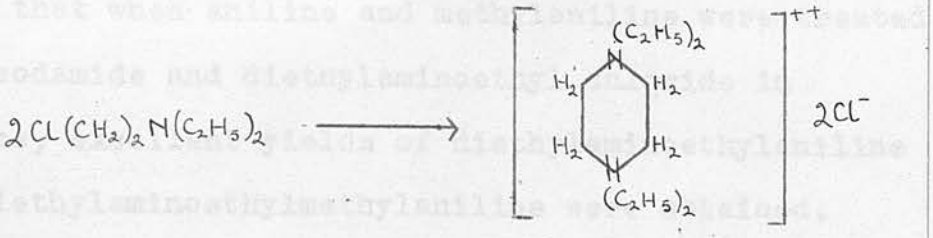


XXXVII

It may also be added that in the analogous reaction between 15-chloro-2:3-benz-γ-carboline and diethylaminoethyl chloride, the carbolinium chloride formed gives an anhydronium base, and that this analyses in agreement with the formula which involves no water of crystallisation. We suggest, then, a similar representation in the present instance.

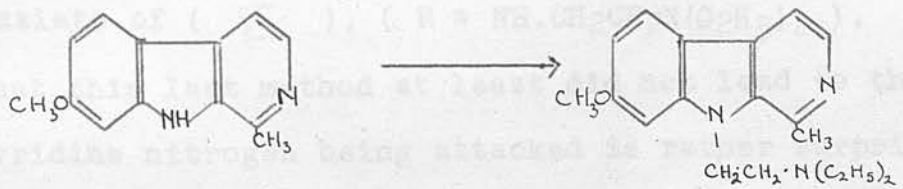
During the treatment of 2:3-benz-γ-carboline with diethylaminoethyl chloride, a white sediment separated from the nitrobenzene solution. This was found to be 1:4-tetraethylpiperazinium dichloride (Gould and King, 1928.), formed by the interaction of two molecules of amine.



The next objective was the diethylaminoethylation of the nitrogen in the pyrrole ring of 2:3-benz-γ-carboline, that is, the preparation of 1-diethylaminoethyl-2:3-benz-γ-carboline.

Eisleb has described a method for the diethylaminoethylation of active methylene groups by means of sodamide and diethylaminochloride in boiling toluene. Under these conditions, tertiary halogenoalkyl- amines or amides do not react with $NaNH_2$ or $NaNH_2 - NH_3$ at 100°; sodamide is thus a very effective reagent for introducing aminoethyl groups into substances which contain hydrogen replaceable by sodium. Eisleb's work was unfortunately published in the 'Berichte' for 1941, which is unavailable to us (Eisleb, 1941.), but British Chemical Abstracts

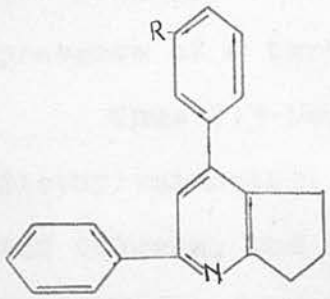
showed that he also used the same process successfully to N-alkylate such compounds as pyrrole, carbazole, 2-methylindole, acridone and diphenylamine. The yield of N-alkylated product in the case of diphenylamine was 81%, as against 40% in the absence of sodamide. Eisleb did not extend his method to the simpler amines, but more recently Dewar (1944) has shown that when aniline and methylaniline were treated with sodamide and diethylaminoethyl chloride in toluene, excellent yields of diethylaminoethylaniline and diethylaminoethylmethylaniline were obtained. Dewar also extended the work to compounds containing two nitrogen atoms; thus he applied the process to harmine (XXXVIII) and he obtained 9-diethylaminoethylharmine (XXXIX). He gave no proof for this formulation.



XXXVIII XXXIX.

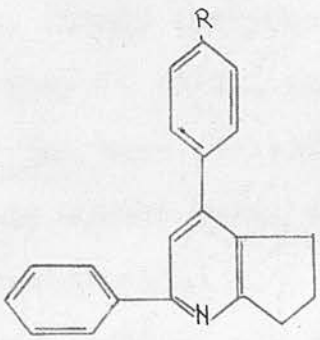
Dewar, in addition, treated the two amines (XL) and (XLI) with sodamide and diethylaminoethyl chloride in toluene, and claimed that they were

converted into the corresponding 5-phenyl-7-(m-β-diethylaminoethylaminophenyl)-4-azahydrindenes ($R=NH_2.CH_2CH_2N(C_2H_5)_2$), which were isolated as their oxalates in 74% and 86% yield.



XL

$R = NH_2$

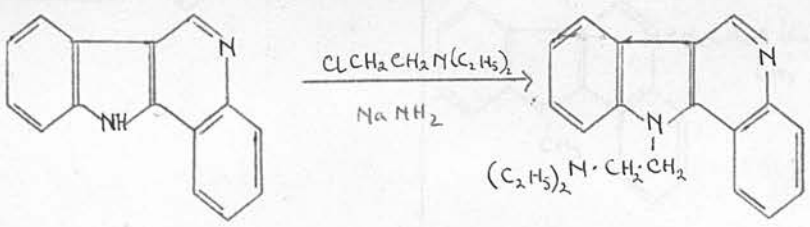


XL-1

In the former case, the chloride - hydrochloride method was also tried in the absence of sodamide, and by it Dewar obtained a 20% yield of the impure oxalate of (XL), ($R = NH.CH_2CH_2N(C_2H_5)_2$). That this last method at least did not lead to the pyridine nitrogen being attacked is rather surprising, though Dewar maintained that neither of these alkylated derivatives could be diazotised, in contrast to their parent amines, thus confirming his conclusions.

We decided to carry out Dewar's modification of Eisleb's method on 2:3-benz-γ-carboline, to verify his assumption that it is the secondary (or primary) nitrogen which is attacked in the presence of a tertiary nitrogen.

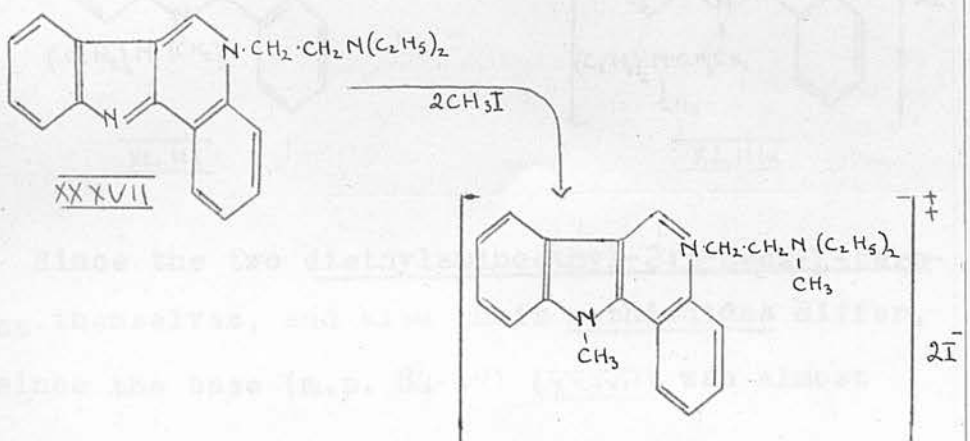
Thus 2:3-benz-γ-carboline was mixed with diethylaminoethyl chloride, finely powdered sodamide and toluene, and heated gently at first, and then at 114° for four hours. The base was extracted from the toluene with dilute acetic acid, from which it was isolated on basification with ammonium hydroxide. After purification, the base melted at 103-4°. It did not lose water on drying in a vacuum desiccator, and analysed correctly for diethylaminoethyl-2:3-benz-γ-carboline. It was quite distinct from 4-diethylaminoethyl-2:3-benz-γ-isocarboline dihydrate prepared previously, indicating that the diethylaminoethyl group is, in fact, on a different nitrogen atom. The equation may thus be written as follows:



XLIII

(e.) The preparation of the methiodides of the two diethylaminoethyl-2:3-benz-ϒ-carboline derivatives.

The substance which we have assumed to be 4-diethylaminoethyl-2:3-benz-ϒ-isocarboline dihydrate (m.p. 84-6°), when dissolved in nitrobenzene was treated with excess methyl iodide. Needles separated from the clear, yellow solution almost immediately, of melting point 263-4°. The crystals were shown by analysis to be diethylaminoethyl-2:3-benz-ϒ-carboline dimethiodide. This product could only have arisen if the original compound were an anhydronium base, the pyrrole nitrogen of which was free for salt formation (see Chemical Introduction). The compound may thus be formulated as (XLII), where one methyl group has added on to the pyrrole nitrogen, and the other, of necessity, on to the terminal nitrogen in the basic side chain.

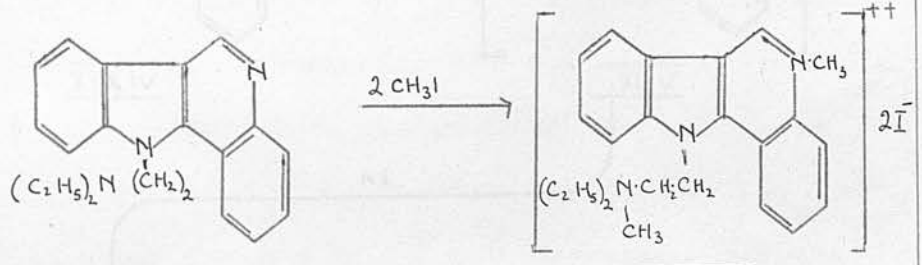


XXXVII

XLII

4-Diethylaminoethyl-2:3-benz-γ-carboline dimethiodide dissolves in water, in which it shows no fluorescence. Its aqueous solution gives no precipitate with ammonium or sodium hydroxides, indicating that no anhydronium base is formed.

The methiodide of the compound prepared by the diethylaminoethylation of 2:3-benz-γ-carboline by Dewar's method, and thought to be 1-diethylaminoethyl-2:3-benz-γ-carboline (m.p. 103-4°), was prepared by treating the base with excess methyl iodide in nitrobenzene as before. The product crystallised from methanol in prisms, and melted at 276-8°. Analysis showed it to be a dimethiodide of diethylaminoethyl-2:3-benz-γ-carboline. A small amount of the product when mixed with 4-diethylaminoethyl-2:3-benz-γ-carboline dimethiodide (m.p. 263-4°) melted at 242-50°, giving a depression of 12°.

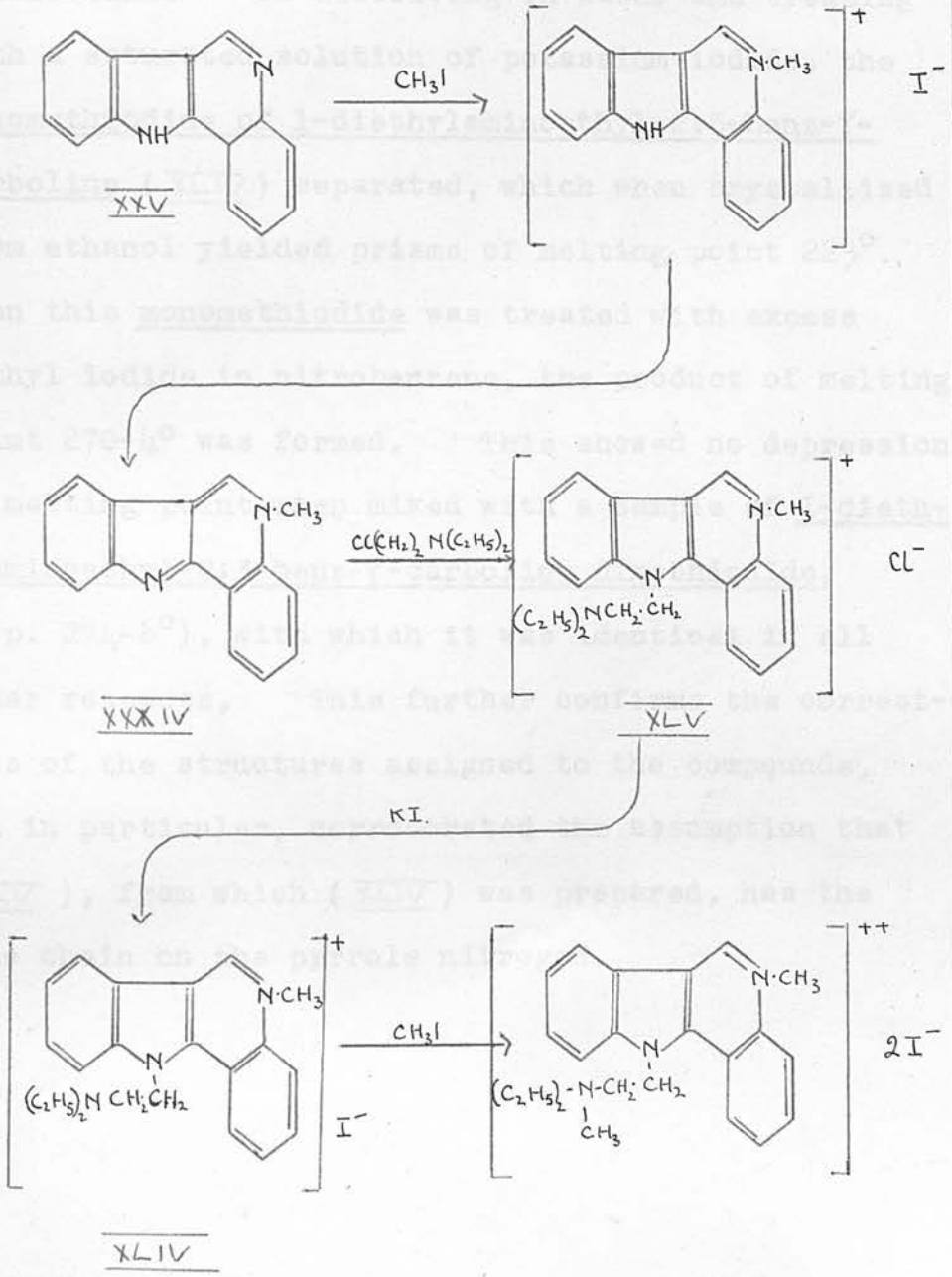


XLIII XLIIIa.

Since the two dietnylaminoethyl-2:3-benz-γ-carbolines themselves, and also their methiodides differ, and since the base (m.p. 84-6°) (XXXVII) was almost

certainly of the formula depicted, it follows that (XLIII) can only have the structure indicated, thus confirming Dewar's original assumption.

In order to investigate the matter further, 1-diethylaminoethylbenz-γ-carboline dimethiodide was prepared by another route according to the following scheme.

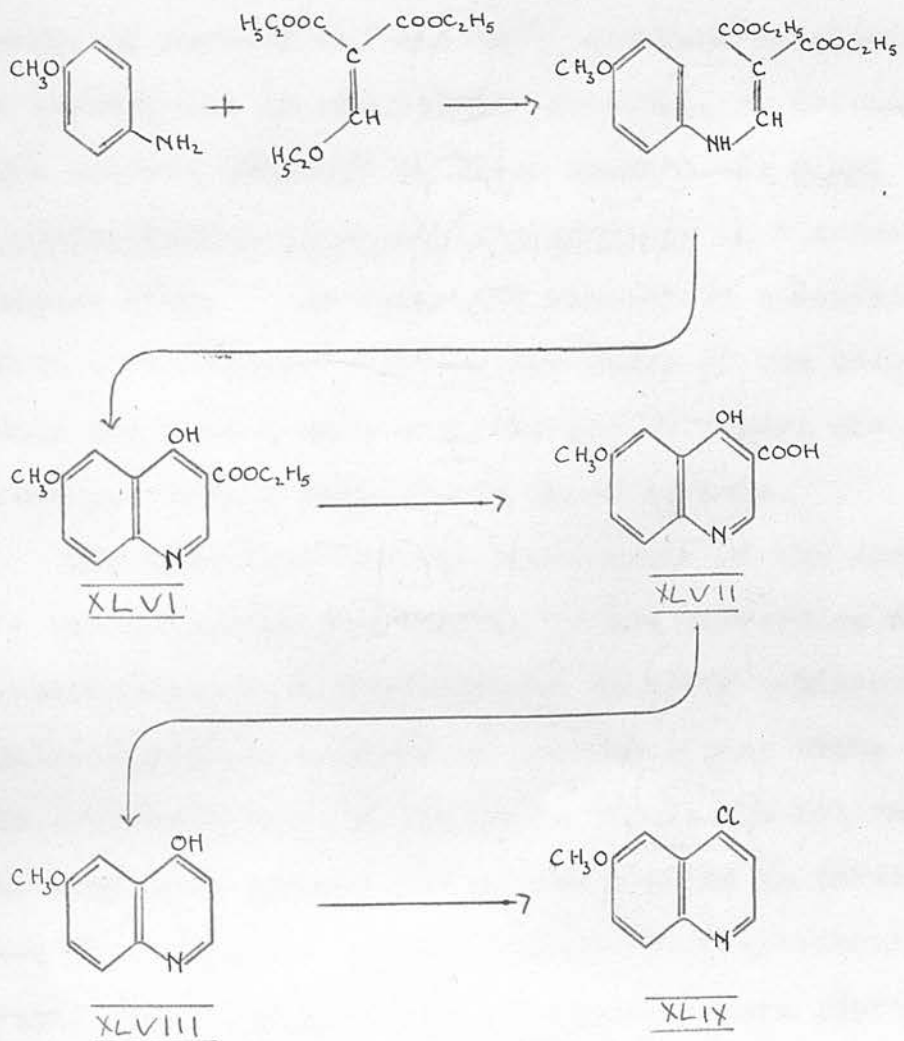


The methiodide of 2:3-benz-γ-carboline was prepared, and treated with ammonium hydroxide to give 4-methyl-2:3-benz-γ-isocarboline (XXXIV). This base on condensation with diethylaminoethyl chloride in nitrobenzene, yielded a crystalline compound, which, if the reaction has gone smoothly, could only be the methochloride of 1-diethylaminoethyl-2:3-benz-γ-carboline. On dissolving in water and treating with a saturated solution of potassium iodide, the monomethiodide of 1-diethylaminoethyl-2:3-benz-γ-carboline (XLIV) separated, which when crystallised from ethanol yielded prisms of melting point 225°. When this monomethiodide was treated with excess methyl iodide in nitrobenzene, the product of melting point 270-4° was formed. This showed no depression in melting point when mixed with a sample of 1-diethylaminoethyl-2:3-benz-γ-carboline dimethiodide, (m.p. 274-6°), with which it was identical in all other respects, This further confirms the correctness of the structures assigned to the compounds, and in particular, corroborated the assumption that (XLV), from which (XLIV) was prepared, has the side chain on the pyrrole nitrogen.

THE SYNTHESIS OF 15-METHOXY-2:3-BENZ-γ-CARBOLINE, AND DERIVATIVE.

(a.) The preparation of 6-methoxy-4-chloroquinoline.

From the experience gained in the preparation of 4-chloroquinoline, we were able to synthesise 6-methoxy-4-chloroquinoline according to the following scheme.



When p-anisidine was warmed on the wwater bath with diethylethoxymethylene malonate, a brown syrup formed, which on cooling partly solidified, forming large, opaque crystals embedded in a syrupy matrix. The product, when purified by crystallisation, melted at 38-40°, and analysed correctly for ethyl α-carbethoxy-β-(p-anisidino-)acrylate. Schofield and Simpson (1946) reported that they were unable to obtain any crystalline material from the crude, oily product; Price and Roberts (1946) recorded a melting point of between -12 and -15°, obtained by placing a thermometer in the melting crystals. Presumably the product obtained by these authors was ethyl α-carbethoxy-β-(p-anisidino-)acrylate in a somewhat impure form. As suggested earlier in connection with an analogous problem, the cause of the discrepancy may have been due to the use of impure diethylethoxymethylene malonate by these authors.

The next step was the cyclisation of the acrylate to the quinoline derivative. The conversion of α-carbethoxy-β-anilinoacrylate to ethyl 4-hydroxyquinoline-3-carboxylate by heating either alone or in a solvent such as liquid paraffin, did not result in very good yields, and it was decided to investigate other and more suitable methods of cyclisation. Price and Roberts (1946) and other workers reported that diphenyl (m.p. 70°), diphenyl ether (m.p. 27°)

and an eutectic mixture of these, commonly known as 'Dowtherm A', (m.p. 12°), are far superior to mineral oil as cyclising media. These solvents boil at approximately 250°, which is optimum for cyclisation, are much less viscous, and are more easily removed from the product. In general, too, the product is formed with much less darkening. In view of these observations, we decided to perform the cyclisation of α-carbethoxy-β-(p-anisidino-)acrylate in diphenyl solution. (diphenyl ether and 'Dowtherm A' being unobtainable at the time, though available later.)

Ethyl α-carbethoxy-β-(p-anisidino-)acrylate was heated in boiling diphenyl for 30 minutes; the ring closed product (XLVI) was isolated from the solution in 80% yield, a very marked increase over the liquid paraffin method. No by-products were isolated from the diphenyl/light petroleum filtrate, even after the use of impure ethyl α-carbethoxy-β-(p-anisidino-)acrylate (cf. Schofield and Simpson). Hydrolysis of ethyl 4-hydroxy-6-methoxyquinoline-3-carboxylate (XLVI) totthe corresponding acid was effected by warming with alkali. The hydroxy acid gives a pink colour with a solution of ferric chloride.

4-Hydroxy-6-methoxyquinoline-3-carboxylic acid (XLVII) was decarboxylated by heating over a free flame. 4-Hydroxy-6-methoxyquinoline (XLVIII) thus obtained imparts a deep red colour to a dilute

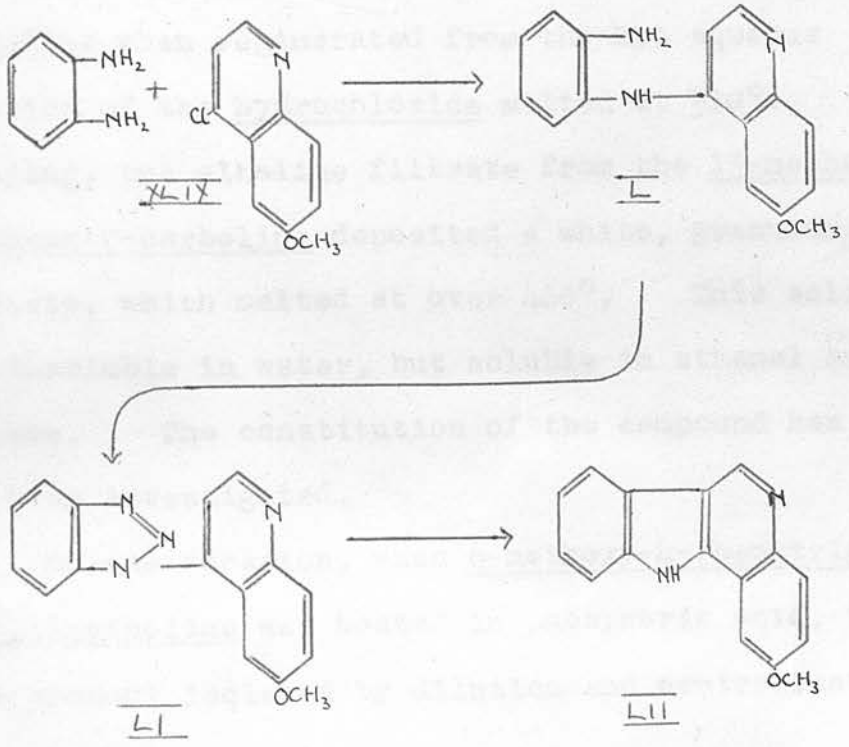
solution of ferric chloride. It was converted into 4-chloro-6-methoxyquinoline (XLIX) by treatment with phosphorus oxychloride and phosphorus pentachloride. The yield of 4-chloro-6-methoxyquinoline was higher than that obtained in the analogous preparation of 4-chloroquinoline from 4-hydroxyquinoline. This may be due to the addition of a molecule of phosphorus pentachloride to the reaction mixture, a reagent which was claimed by American workers to increase the yield of 4-chloroquinolines.

Once the conditions for these stages in the synthesis of 4-chloro-6-methoxyquinoline had been established, it was decided to carry out a 'continuous' experiment for the preparation of the intermediate, as described by Price and Roberts (1946) for the preparation of 4:7-dichloroquinoline. This process enables one to obtain the compound relatively quickly and without isolation at every stage. The main difference from the slower method is that the ester obtained by cyclising in diphenyl is hydrolysed without separating from the solvent, and the resulting hydroxy acid is then decarboxylated, and the product treated with phosphorus oxychloride in the same solution. Details of the procedure are given in the experimental section. In our hands, the process worked well up to the last stage, until the isolation of 4-chloro-6-methoxyquinoline from the

diphenyl/diphenyl ether/phosphorus oxychloride solution. As this proved difficult, it was found best to interrupt the procedure before treatment with phosphorus oxychloride; the 4-hydroxy-6-methoxyquinoline was then isolated and converted into 4-chloro-6-methoxyquinoline in the usual way.

(b.) The synthesis of 15-methoxy-2:3-benz-γ-carboline and derivatives from 4-chloro-6-methoxyquinoline.

15-Methoxy-2:3-benz-γ-carboline (LII) was prepared by decomposing the triazole (LI), which was obtained from 6-methoxy-4-o-aminophenylaminoquinoline in the following way.

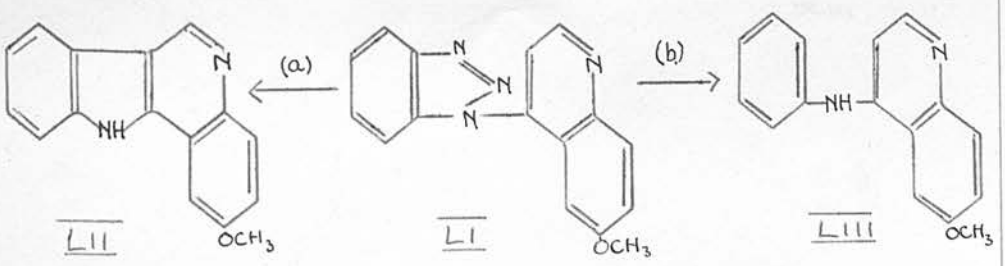


6-Methoxy-4-o-aminophenylaminoquinoline was prepared in 47% yield when 4-chloro-6-methoxyquinoline (XLIX) and o-phenylenediamine were condensed together under reduced pressure. The base was liberated from the hydrochloride by treatment with alkali, and was purified by crystallisation from benzene. 6-Methoxy-4-o-aminophenylaminoquinoline was converted into 6-methoxy-4-(benztriazolyl-1')quinoline hydrochloride by treatment with sodium nitrite in cold, dilute hydrochloric acid. The free base was isolated from the hydrochloride by treatment with alkali.

6-Methoxy-4-(benztriazolyl-1')quinoline was decomposed into 15-methoxy-2:3-benz-γ-carboline by heating in phosphoric acid. The base proved difficult to purify, and it was at first characterised by its hydrochloride. 15-Methoxy-2:3-benz-γ-carboline when regenerated from the hot aqueous solution of the hydrochloride melted at 310°. On standing, the alkaline filtrate from the 15-methoxy-2:3-benz-γ-carboline deposited a white, granular precipitate, which melted at over 400°. This solid was insoluble in water, but soluble in ethanol and benzene. The constitution of the compound has not yet been investigated.

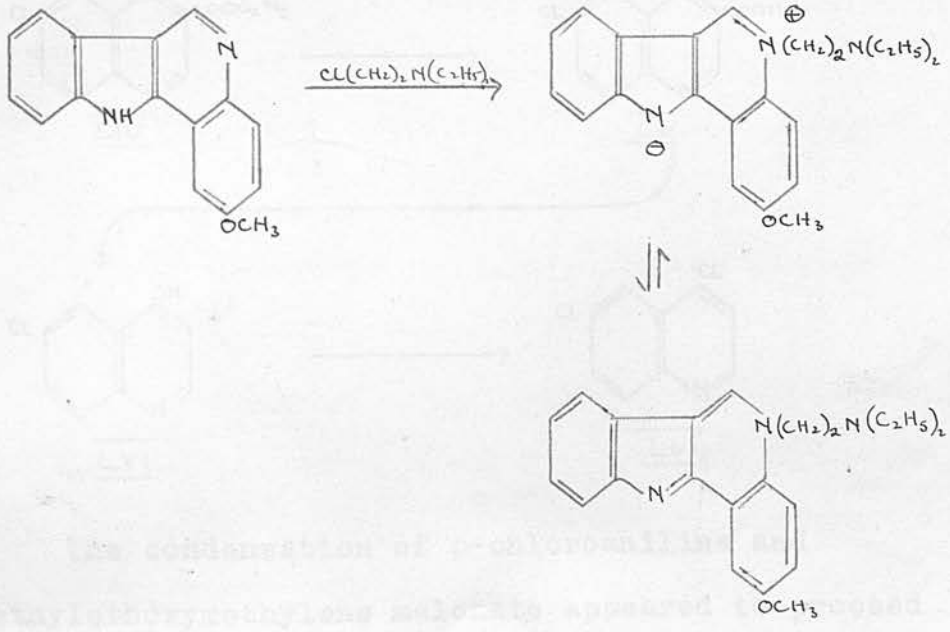
On one occasion, when 6-methoxy-4-(benztriazolyl-1')quinoline was heated in phosphoric acid, the main product isolated by dilution and neutralisation

of the reaction mixture, was found to melt at 198-200°. The compound was distinct from 6-methoxy-4-o-aminophenylaminoquinoline (L),(m.p.192°), as was shown by a mixed melting point. The product was later shown to be 6-methoxy-4-anilinoquinoline (LIII), (m.p. 220°). That any of this compound should have resulted from 6-methoxy-4-(benztriazolyl-1')quinoline (LI) by simple heating in phosphoric acid is surprising, but that it should be the main product of the reaction is even more extraordinary. Cowdrey and Davies (1949), investigating the kinetics and mechanism of the Sandmeyer reaction for the replacement of diazonium groups by halogen, have shown that although the symmetrical azo compound is the major by-product, minor by-products include the hydrocarbon ArH, the phenol ArOH and the biaryl Ar.Ar. In the case under review, the preparation of 15-methoxy2:3-benz-γ-carboline (LII) from the benztriazole (LI), might be said to be analogous to the formation of Ar.Ar, and that of 4-anilino-6-methoxyquinoline (LIII) to the formation of ArH, according to the equations (a.) and (b.).



It is nevertheless very difficult to understand how the latter reaction could occur to any considerable extent in the absence of a reducing agent, and one can only surmise that there was a reducing contaminant in the reactants.

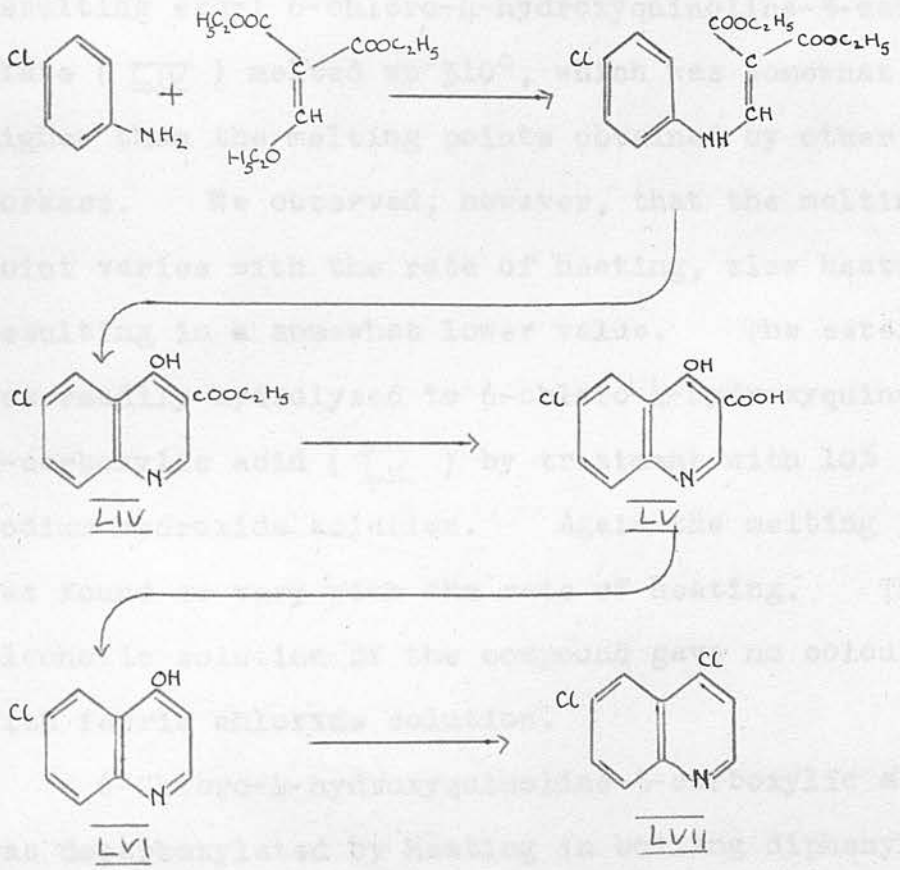
15-Methoxy-2:3-benz-γ-carboline when treated with diethylaminoethyl chloride in nitrobenzene afforded a crystalline hydrochloride, from which an oily base was regenerated. Attempts to crystallise this product were unsuccessful, and 4-diethylaminoethyl-15-methoxy-2:3-benz-γ-isocarboline was characterised as the dinitrobenzoate.



THE SYNTHESIS OF 15-CHLORO-2:3-BENZ-γ-CARBOLINE AND DERIVATIVES.

(a.) The preparation of 4:6-dichloroquinoline.

4:6-Dichloroquinoline was obtained according to the following scheme.



The condensation of p-chloroaniline and diethylethoxymethylene malonate appeared to proceed more slowly than in the case of aniline and p-anisidine, and longer heating was found necessary by Duffin and Kendall (1948), and by Tarbell (1946). The latter

found it advantageous to heat the reactants to a temperature of 120-130°, though we carried out the reaction at 100°. These authors state the melting point of the compound to be 71°, in agreement with us.

The acrylate was cyclised by heating in a solution of boiling diphenyl/diphenyl ether. The resulting ethyl 6-chloro-4-hydroxyquinoline-3-carboxylate (LIV) melted at 310°, which was somewhat higher than the melting points obtained by other workers. We observed, however, that the melting point varies with the rate of heating, slow heating resulting in a somewhat lower value. The ester was readily hydrolysed to 6-chloro-4-hydroxyquinoline-3-carboxylic acid (LV) by treatment with 10% sodium hydroxide solution. Again the melting point was found to vary with the rate of heating. The alcoholic solution of the compound gave no colour with ferric chloride solution.

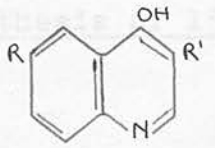
6-Chloro-4-hydroxyquinoline-3-carboxylic acid was decarboxylated by heating in boiling diphenyl/diphenyl ether solution. Decarboxylation proceeded somewhat slowly, and heating had to be maintained for 3 hours, after which period the 6-chloro-4-hydroxyquinoline was isolated in good yield. The compound was also prepared by a continuous process, in which only the final end product was isolated.

The method was almost identical with that used in the preparation of 4-hydroxy-6-methoxyquinoline, differing only in details of working up. (see experimental section.) Unlike 4-hydroxyquinoline and 4-hydroxy-6-methoxyquinoline, 6-chloro-4-hydroxyquinoline did not give a red colour with ferric chloride solution.

6-Chloro-4-hydroxyquinoline (LVI) was converted to 4:6-dichloroquinoline (LVII) by treatment with phosphorus oxychloride and pentachloride in 87% yield. The compound melted at 102-4°, in agreement with Tarbell (1946), and Riegel et al. (1946), and with Bachman and Cooper (1947) who prepared it in 35% yield by the Meisenheimer procedure from the N-oxide. The superiority of the present method is thus easily seen.

The various observations on the colour reaction between 4-hydroxyquinolines and ferric chloride are summarised here. (See table on next page.)

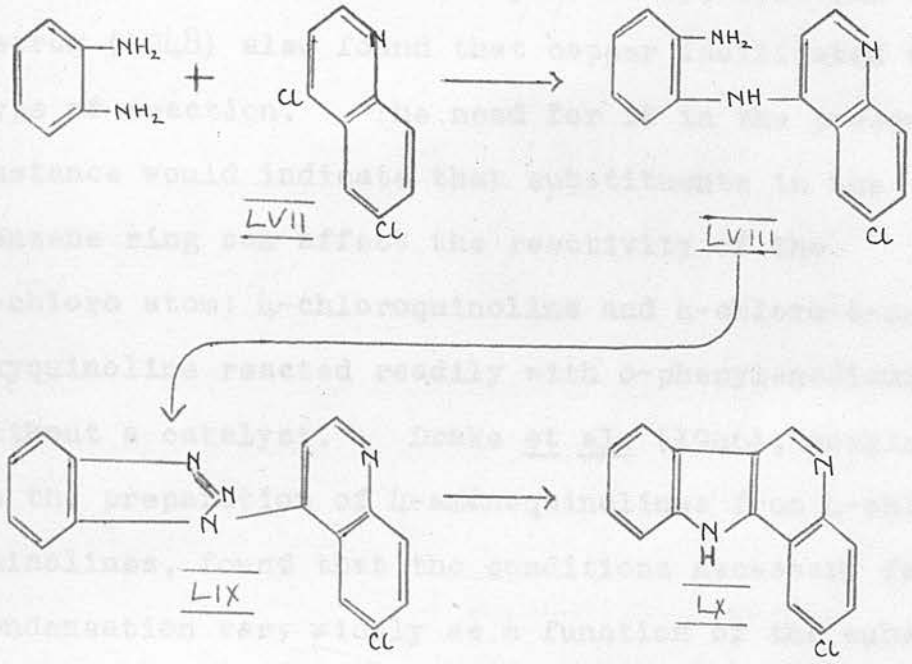
As will be seen, all the p-anisidino compounds give colours, but none of the p-chloro derivatives do so. In addition, the colour reaction was tried on 4-hydroxy-3-phenylcarbamylquinoline; this compound gave no colour whatsoever, in conformity with the results of Schofield and Simpson.



R	R'	Colour
H	H	red
H	$COOC_2H_5$	none
H	COOH	none
H	$CONHC_6H_5$	none
OCH_3	H	red
OCH_3	$COOC_2H_5$	red
OCH_3	COOH	red
Cl	H	none
Cl	$COOC_2H_5$	none
Cl	COOH	none

(b.) The synthesis of 15-chloro-2:3-benz-γ-carboline.

The following procedure for the synthesis of 15-chloro-2:3-benz-γ-carboline was adopted.



No reaction appeared to take place when 4:6-dichloroquinoline (LVII) and o-phenylenediamine were heated together at 140° under a pressure of 20 mm., though a considerable amount of the dichloroquinoline sublimed, and collected in the neck of the flask. Even when this sublimate was returned to the body of the flask, and the contents were again ~~again~~ heated for a further period, no reaction resulted, and the reactants were isolated unchanged. On repeating the experiment in the presence of a trace of copper bronze, a vigorous reaction took

place almost immediately, and the solid hydrochloride of 6-chloro-4-o-aminophenylaminoquinoline was formed, which afforded 6-chloro-4-o-aminophenylaminoquinoline on basification. On one occasion, a by-product was obtained, the constitution of which will be discussed on page 100. As mentioned previously, Holt and Petrow (1948) also found that copper facilitated this type of reaction. The need for it in the present instance would indicate that substituents in the benzene ring can affect the reactivity of the 4-chloro atom; 4-chloroquinoline and 4-chloro-6-methoxyquinoline reacted readily with o-phenylenediamine without a catalyst. Drake et al. (1946), working on the preparation of 4-aminoquinolines from 4-chloroquinolines, found that the conditions necessary for condensation vary widely as a function of the substitution. They observed that 4-chloroquinolines bearing a substituent in the 2- or 3- position, require longer times and higher temperatures for complete reaction than do 4-chloroquinolines bearing their substituents in the benzene ring. That these other substituents themselves, and their position in the carbocyclic ring, can also affect the issue has been borne out by the observations of several American workers, in conformity with our results.

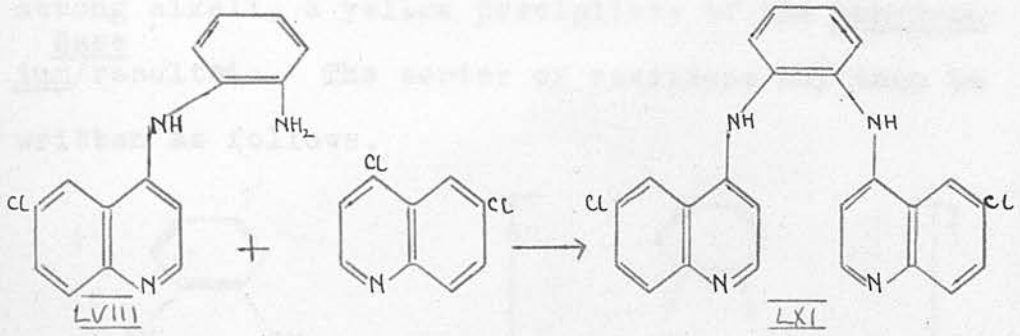
When a solution of 6-chloro-4-o-aminophenylaminoquinoline in dilute hydrochloric acid was treated

with sodium nitrite, 6-chloro-4-(benztriazolyl-1')-quinoline (LIX) separated. This base, when heated in boiling syrupy phosphoric acid, yielded 15-chloro-2:3-benz-γ-carboline (LX) in 70% yield. Unlike either 2:3-benz-γ-carboline or 15-methoxy-2:3-benz-γ-carboline, the base is only sparingly soluble in dilute or concentrated mineral acids. Its solution in methanol or in concentrated sulphuric acid showed no fluorescence under the arc lamp.

(c.) The nature of the by-product isolated during the synthesis of 15-chloro-2:3-benz-γ-carboline.

On one occasion during the condensation of 4:6-dichloroquinoline and o-phenylenediamine, a product was formed which was only partially soluble in ethanol. When the 6-chloro-4-o-aminophenyl-aminoquinoline was extracted with this solvent, a residue was left melting at approximately 300°. The insoluble portion did not dissolve in ethanol, water, benzene, acetone or ether, but it was soluble in acetic acid, from which it could be precipitated by alkali. It was also soluble in nitrobenzene, from which it was crystallised, and showed a melting point of 342°. The solubilities of the compound suggested a relatively large molecule with basic

properties, and since it contained halogen the only possible by-product appeared to be N:N'-bis(6-chloroquinolyl)-o-phenylenediamine (LXI). This was confirmed by analysis, and by the following synthesis

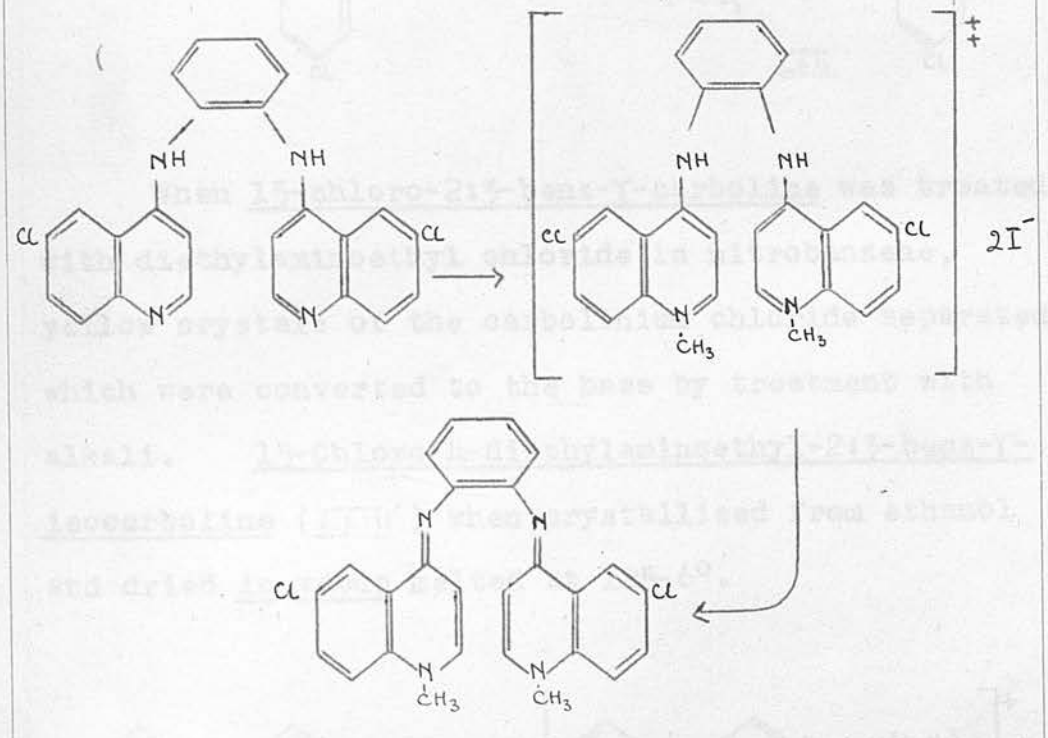


LVIII LXI

When 6-chloro-4-o-aminophenylaminoquinoline and 4:6-dichloroquinoline were heated together under reduced pressure in presence of a little copper powder, a hydrochloride formed, which on basification yielded a product of melting point 342°. This was identical with the by-product under discussion.

N:N'-bis(6-chloroquinolyl)-o-phenylenediamine formed a methosulphate on treatment with dimethyl sulphate in nitrobenzene. The salt was converted to the methiodide on treatment with potassium iodide. The product was found to be the dihydrate of the dimethiodide of N:N'-bis(6-chloroquinolyl)-o-phenylenediamine. Crystallisation of this compound was made difficult by a red, flocculent precipitate, which separated as a film over the pure, yellow crystals. Isolation of the product showed it to

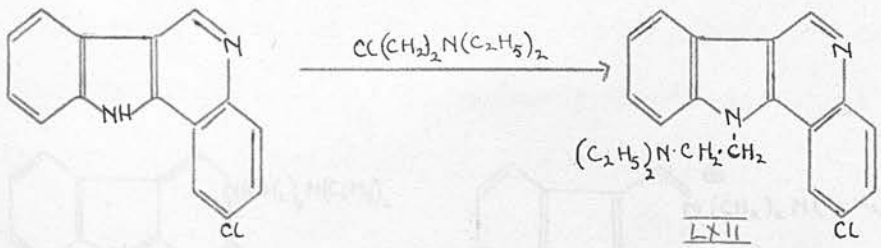
have a melting point of 190°, but when redissolved and seeded with the yellow crystals, a homogeneous mass appeared again on cooling, and had melting point of 330°. The dimethiodide was soluble in water, and when the aqueous solution is treated with strong alkali, a yellow precipitate of the anhydron-base ium resulted. The series of reactions may then be written as follows.



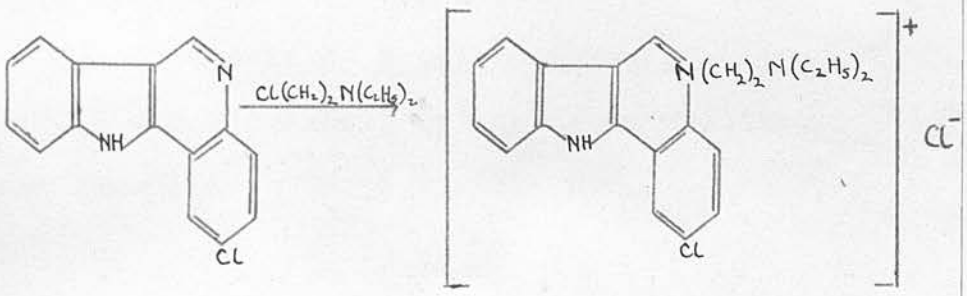
(d.) The preparation of derivatives of 15-chloro-2:3-benz-γ-carboline.

15-Chloro-2:3-benz-γ-carboline on treatment with methyl iodide in nitrobenzene yielded a methiodide, whose aqueous solution on basification afforded 15-chloro-4-methyl-2:3-benz-γ-isocarboline.

15-Chloro-1-diethylaminoethyl-2:3-benz-γ-carboline (LXII) was prepared by heating 15-chloro-2:3-benz-γ-carboline, diethylaminoethyl chloride and sodamide in toluene at 110° for 4 hours. The base is a yellow crystalline compound melting at 114-5°.

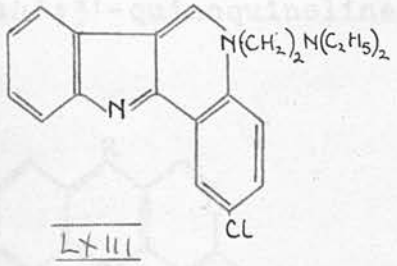


When 15-chloro-2:3-benz-γ-carboline was treated with diethylaminoethyl chloride in nitrobenzene, yellow crystals of the carbolinium chloride separated, which were converted to the base by treatment with alkali. 15-Chloro-4-diethylaminoethyl-2:3-benz-γ-isocarboline (LXIII) when crystallised from ethanol and dried in vacuo melted at 125-6°.

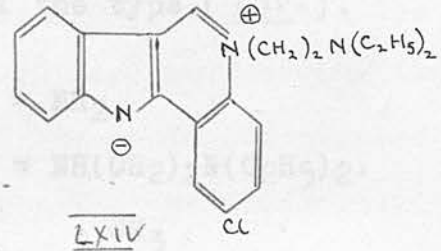


This compound is a typical anhydronium base, and as mentioned previously, is to be regarded as a a resonance hybrid between the two structures

(LXIII) and (LXIV). Like 4-diethylaminoethyl-2:3-benz-γ-isocarboline, this base is hygroscopic, and it is only after drying in vacuo at 80° that the anhydro compound is obtained.



LXIII

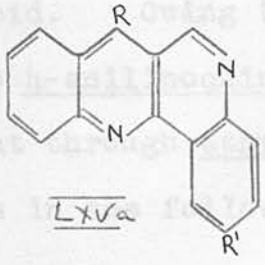


LXIV

STUDIES IN THE 2:3:4':3'-QUINOQUINOLINE FIELD.

(a.) The synthesis of 4-chloro-2:3:4':3'-quinoquinoline.

As mentioned in the introduction, it was considered desirable to prepare basic derivatives of 2:3:4':3'-quinoquinolines of the type (LXVa).



LXVa

R = NH_2.

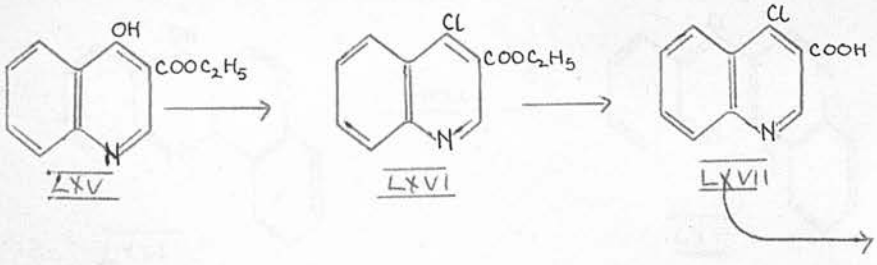
= $NH(CH_2)_2N(C_2H_5)_2$.

= $NH.CH(CH_3)(CH_2)_3N(C_2H_5)_2$.

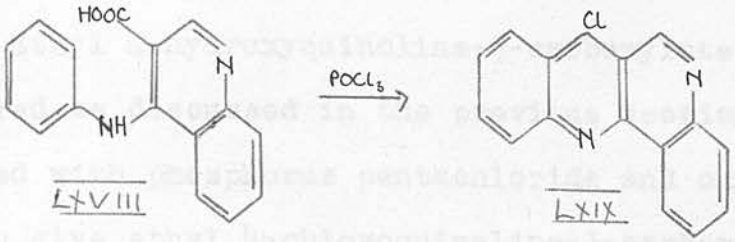
R' = H, OCH_3, Cl.

For this purpose, it was necessary to prepare 4-chloro-2:3:4':3'-quinoquinolines, as these compounds when treated the appropriate amines, should yield bases of the desired type.

The synthesis of 4-chloro-2:3:4':3'-quinoquinoline was approached by the method indicated by the formulae (LXV) to (LXIX).

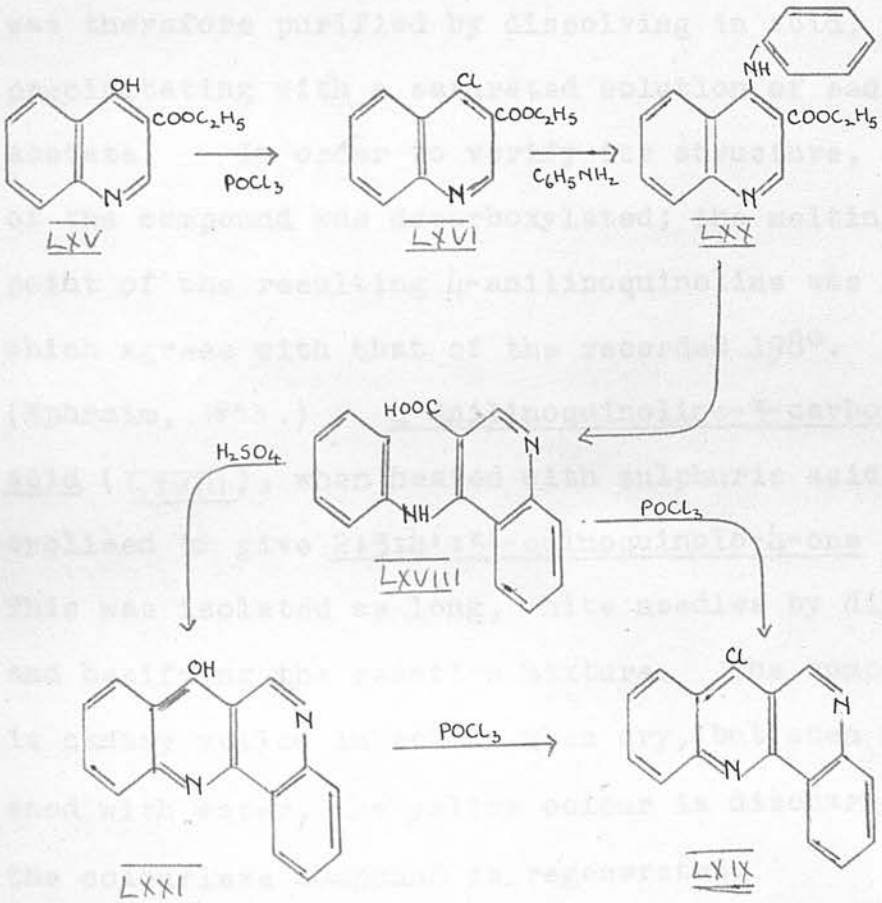


LXV LXVI LXVII



LXVIII LXIX

In this scheme, however, we were unable to prepare 4-chloroquinoline-3-carboxylic acid (LXVII); it was found that at conditions required for the hydrolysis of the ester group to the acid, the chlorine atom was also hydrolysed, with the subsequent formation of 4-hydroxyquinoline-3-carboxylic acid. Owing to this fact, we could not proceed to 4-anilinoquinoline-3-carboxylic acid directly, but through ethyl 4-anilinoquinoline-3-carboxylate as in the following series of reactions.



LXV LXVI LXX

LXVIII

LXXI LXIX

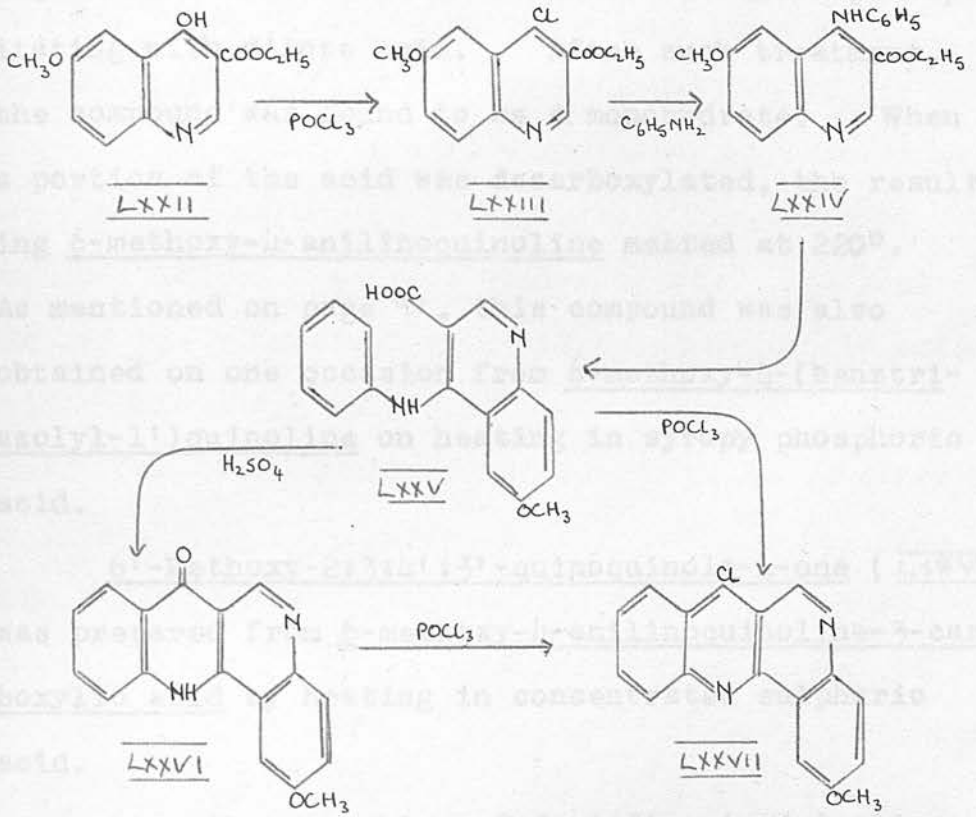
Ethyl 4-hydroxyquinoline-3-carboxylate (LXV) prepared as discussed in the previous section, reacted with phosphorus pentachloride and oxychloride to give ethyl 4-chloroquinoline-3-carboxylate. (LXVI). This compound readily reacted with an equimolecular amount of aniline to give ethyl 4-anilinoquinoline-3-carboxylate hydrochloride, from which the base was obtained on basification. Ethyl 4-anilinoquinoline-3-carboxylate (LXX) on hydrolysis with alcoholic sodium hydroxide afforded 4-anilinoquinoline-3-carboxylic acid (LXVIII). This compound resisted all attempts at crystallisation, its hot solution either cooling as a gel, or depositing a flocculent precipitate. The product was therefore purified by dissolving in acid, and precipitating with a saturated solution of sodium acetate. In order to verify its structure, some of the compound was decarboxylated; the melting point of the resulting 4-anilinoquinoline was 196-8°, which agrees with that of the recorded 198°. (Ephraim, 1893.) 4-Anilinoquinoline-3-carboxylic acid (LXVIII), when heated with sulphuric acid, cyclised to give 2:3:4':3'-quinoquinolo-4-one (LXXI). This was isolated as long, white needles by diluting and basifying the reaction mixture. The compound is canary yellow in colour when dry, but when moistened with water, the yellow colour is discharged and the colourless compound is regenerated.

4-Chloro-2:3:4':3'-quinoquinoline (LXIX) was prepared from 2:3:4':3'-quinoquinolo-4-one (LXXI) and from 4-anilinoquinoline-3-carboxylic acid (LXVIII) by treating these compounds with phosphorus oxychloride and pentachloride. When the reaction was complete, the excess oxychloride was removed by distillation, and the residue triturated with chilled, 20% sodium hydroxide. Great care was taken to ensure that the product was in a finely divided state, sotthat no acidity had a chance to develop on its coming in contact with water. In this way, hydrolysis to the quinoquinolone was reduced to the minimum, as traces of hydrochloric acid act as a catalyst in this conversion. The product when digested with hot benzene in presence of a pellet of potassium hydroxide, was found to be a mixture of insoluble 2:3:4':3'-quinoquinolone, and of 4-chloro-2:3:4':3'-quinoquinoline (LXIX), which separated from the cold benzene filtrate.

4-Chloro-2:3:4':3'-quinoquinoline is readily hydrolysed to 2:3:4':3'-quinoquinolone in the presence of acid; it is stable to alkali, and may be refluxed in ethanol in the presence of a trace of water without hydrolysis taking place. In this respect, its properties are very similar to those of 5-chloroacridine, and various chlorobenzquinolines and chloropyridoacridines.

(b.) THE SYNTHESIS OF 6'-METHOXY-4-CHLORO-2:3:4':3'-QUINOQUINOLINE.

6'-Methoxy-4-chloro-2:3:4':3'-quinoquinoline (LXXVII) was prepared according to the following scheme.



LXXII LXXIII LXXIV LXXV LXXVI LXXVII

Ethyl 4-hydroxy-6-methoxyquinoline-3-carboxylate (LXXII), prepared as described on page 88, when treated with phosphorus oxychloride and pentachloride yielded ethyl 6-methoxy-4-chloroquinoline-3-carboxylate (LXXIII). This compound, when intimately mixed with an equimolecular amount of aniline, reacted immediately with evolution of heat to give ethyl 6-methoxy-4-anilinoquinoline-3-carboxylate hydrochloride, from which the base was isolated by basification.

Ethyl 6-methoxy-4-anilinoquinoline-3-carboxylate (LXXIV) was hydrolysed to 6-methoxy-4-anilinoquinoline-3-carboxylic acid (LXXV). Attempts to crystallise the compound were unsuccessful, and purification was accomplished by repeatedly dissolving the gel in dilute sodium carbonate and reprecipitating with dilute acid. After such treatment, the compound was found to be a monohydrate. When a portion of the acid was decarboxylated, the resulting 6-methoxy-4-anilinoquinoline melted at 220°. As mentioned on page 92, this compound was also obtained on one occasion from 6-methoxy-4-(benztriazolyl-1')quinoline on heating in syrupy phosphoric acid.

6'-Methoxy-2:3:4':3'-quinoquinolo-4-one (LXXVI) was prepared from 6-methoxy-4-anilinoquinoline-3-carboxylic acid by heating in concentrated sulphuric acid.

6'-methoxy-4-chloro-2:3:4':3'-quinoquinoline (LXXVII) was obtained from 6-methoxy-4-anilinoquinoquinoline-3-carboxylic acid (LXXV) by heating in phosphorus oxychloride, and working up with strong alkali as before. This chloro compound withstands prolonged heating in dilute alkali, but is converted to the quinoquinolone on heating with dilute acids.

The conversion of 6'methoxy-2:3:4':3'-quinoquinolo-4-one into 6'-methoxy-4-chloro-2:3:4':3'-

quinoquinoline with phosphorus pentachloride and oxychloride was carried out in presence of a trace of 'Cetavlon' (cetyltrimethylammonium bromide). The idea of adding this surface active agent was suggested by the U.S. Patent 2394 279, Feb. 5th. This states that in the presence of a trace of phosphorus pentachloride, the condensation of 2-hydroxy-3-naphthoic acid with amines gave anilides, the yield of which was very markedly increased by the addition of a surface active agent. To test whether the conversion of 2-hydroxy-3-naphthoic acid into 2-chloro-3-naphthoic acid on treatment with phosphorus oxychloride and pentachloride might be affected in the same way, Cairns and Kermack (unpublished report) added 'Cetavlon' to this reaction mixture, and increased the yield of product from 30% to 70%. In the present instance, two experiments were conducted for the conversion of 6'-methoxy-2:3:4':3'-quinoquinolo-4-one into 6'-methoxy-4-chloro-2:3:4':3'-quinoquinoline, in one of which a trace of 'Cetavlon' was present. Thus, crude 6'methoxy-2:3:4':3'-quinoquinolo-4-one when heated with phosphorus pentachloride and oxychloride, gave 6'-methoxy-4-chloro-2:3:4':3'-quinoquinoline in 31% yield, and unchanged (or regenerated) quinoquinolone in 34% yield, as compared with 47% yield of chloro compound

when 'Cetavlon' was present. The crude product obtained from this latter experiment was also found to be considerably purer than that obtained from the previous one, verifying the results of Cairns and Kermack. The mechanism of the phenomenon is not known. The yield of chloro compound from the treatment of the quinoquinolone is not good in either case, and this is in agreement with results of Hutchison and Kermack (1946) in the conversion of 2:8-dichloro-3:4:2'3'-pyridoacridone to the 5-chloro compound, and of Bachman and Barker (1949), who attempted to prepare 9-chloropyridoquinoline from the corresponding oxy-compound.

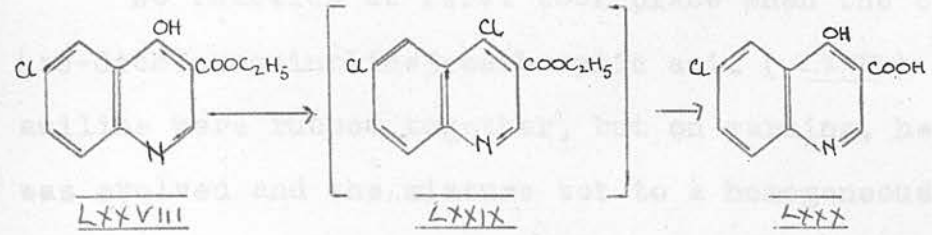
An attempt was also made to prepare 6-methoxy-4-chloroquinoline-3-carboxylic acid from ethyl 6-methoxy-4-chloroquinoline-3-carboxylate by hydrolysis with acid and alkali under various conditions of temperature and concentration. In no case could the chloro-acid be isolated, 6-methoxy-4-hydroxyquinoline-3-carboxylic acid being always obtained. In a further attempt to prepare this chloro-acid, 6-methoxy-4-hydroxyquinoline was treated with phosphorus oxychloride and pentachloride in the expectation of forming the acid chloride of 6-methoxy-4-chloroquinoline-3-carboxylic acid, which on mild hydrolysis might be expected to give 6-methoxy-4-chloroquinoline-3-carboxylic acid. However, in this case a compound

was isolated whichwwas insoluble in alkali, but soluble in acid solution. It was thought to be a chlorinated compound, and its nature was not further investigated.

(c.) THE SYNTHESIS OF 4:6'-DICHLORO-2:3:4':3'-QUINOQUINOLINE.

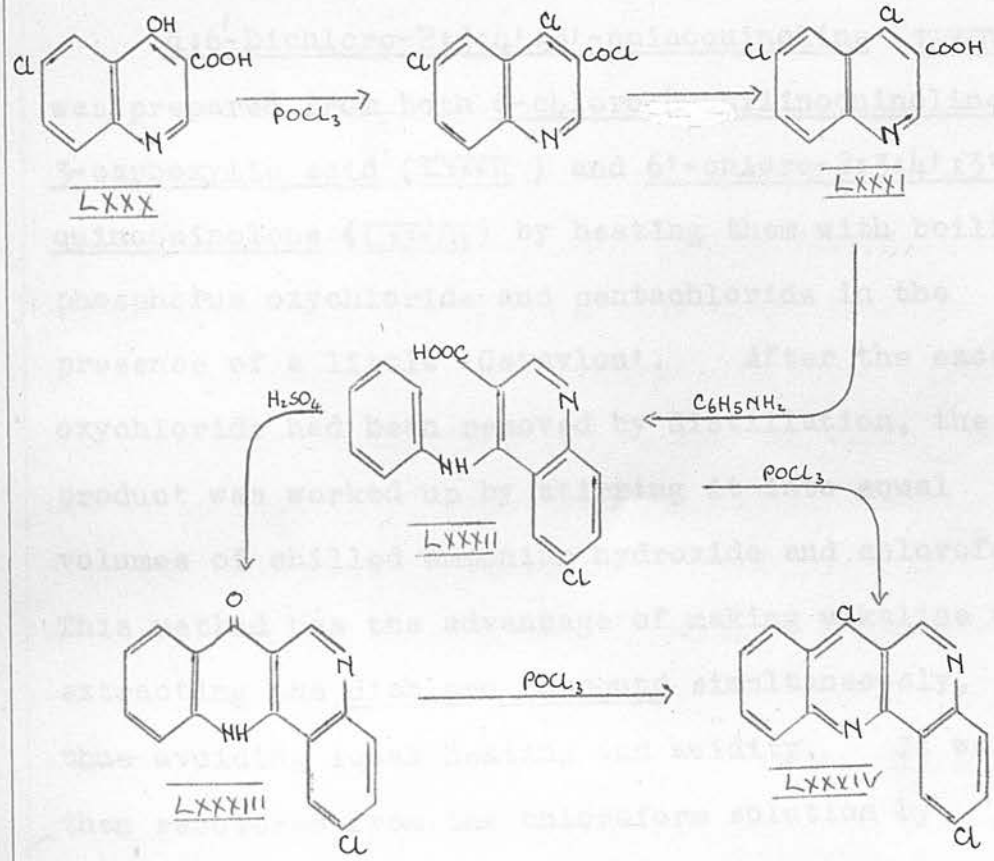
It was found possible to prepare 4:6'-dichloro-2:3:4':3'-quinoquinoline through somewhat different intermediates than those used in the preparation of 4-chloro- and 6'-methoxy-4-chloro-2:3:4':3'-quinoquinolines. This was due to the chlorine atom in the 6-position of the quinoline so inhibiting the reactivity of the 4-chloro atom as to allow the preparation of 4:6-dichloroquinoline-3-carboxylic acid from 6-chloro-4-hydroxyquinoline-3-carboxylica acid.

An attempt was first made to prepare ethyl 4:6-dichloroquinoline-3-carboxylate (LXXIX) by treating ethyl 6-chloro-4-hydroxyquinoline-3-carboxylate (LXXVIII) with phosphorus oxy- and pentachloride. During the working up of the reaction mixture, however, the temperature rose somewhat more than was anticipated, and 6-chloro-4-hydroxyquinoline-3-carboxylic acid resulted (LXXX).



LXXVIII LXXIX LXXX

When this acid (LXXX) was treated with phosphorus oxy- and pentachloride, and poured into dilute carbonate solution with cooling, a product resulted which was distinct from 6-chloro-4-hydroxyquinoline, and which was shown to be 4:6-dichloroquinoline-3-carboxylic acid (LXXXI). The complete synthesis may then be written as follows.



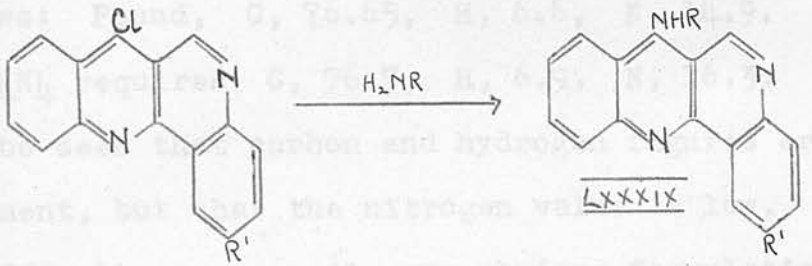
No reaction at first took place when the crude 4:6-dichloroquinoline3-carboxylic acid (LXXXI) and aniline were rubbed together, but on warming, heat was evolved and the mixture set to a homogeneous gum. 6-Chloro-4-anilinoquinoline-3-carboxylic acid (LXXXII) was obtained from this on basification. Like the other two 4-anilinoquinoline-3-carboxylic acids, this compound could not be crystallised.

6'-Chloro-2:3:4':3'-quinoquinolo-4-one (LXXXIII) was prepared by cyclising 6-chloro-4-anilinoquinoline-3-carboxylic acid (LXXXII) in concentrated sulphuric acid. The compound melted above 360°, which high temperature is common to all these quinoquinolones.

4:6'-Dichloro-2:3:4':3'-quinoquinoline (LXXXIV) was prepared from both 6-chloro-4-anilinoquinoline-3-carboxylic acid (LXXXII) and 6'-chloro-2:3:4':3'-quinoquinolone (LXXXIII) by heating them with boiling phosphorus oxychloride and pentachloride in the presence of a little 'Cetavlon'. After the excess oxychloride had been removed by distillation, the product was worked up by stirring it into equal volumes of chilled ammonium hydroxide and chloroform. This method has the advantage of making alkaline and extracting the dichloro compound simultaneously, thus avoiding local heating and acidity. It was then recovered from the chloroform solution by removal of the solvent in vacuo,

(d.) THE PREPARATION OF BASIC DERIVATIVES OF 2:3:4':3'-QUINOQUINOLINES.

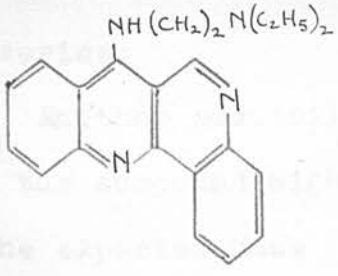
As mentioned at the beginning of this section, 4-chloro-2:3:4':3'-quinoquinoline, 6'-methoxy-4-chloroquinoquinoline and 4:6'-dichloro-2:3:4':3'-quinoquinoline were prepared in order that these compounds when treated with amines should yield bases of the type (LXXXIX).

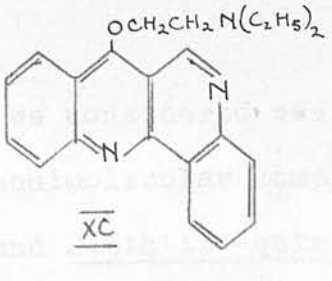


LXXXIX

The method used for the attempted preparation of these compounds was almost identical with that described by Dobson and Kermack (1946), and Hutchison and Kermack (1948), differing only slightly in details of working up. The 4-chloro compound was added to a mixture of dry phenol and dry amine, and heated at 100° for 2 hours. The cooled phenolic solution was poured into 2N sodium hydroxide to yield an oil which was extracted with ether. The ethereal solution was extracted with dilute acid and basified to yield the product. This was either filtered off or reextracted with ether, from which the base was obtained by evaporation of solvent.

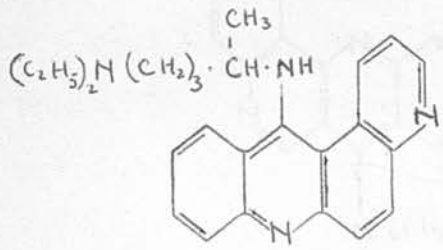
An attempt was made to condense 4-chloro-2:3:4':3'-quinoquinoline with diethylaminoethylamine in this way. The product was a ~~white~~ YELLOW base, which when recrystallised from light petroleum melted with previous softening at 80-1°. The melting point when taken on a Köfler type hot stage apparatus was found to soften at 45°, melt at 60-5°, solidify at 70-5° and melt finally at 80-1°. Chromatography on alumina failed to sharpen the melting point. The analytical results for the compound were as follows: Found, C, 76.65, H, 6.6, N, 14.9. $C_{22}H_{24}N_4$ requires C, 76.7, H, 6.9, N, 16.3. It will be seen that carbon and hydrogen figures are in agreement, but that the nitrogen value is low. It is difficult to reconcile any obvious formulation for the compound with these results, but it is interesting to note that the carbon, hydrogen and nitrogen figures are in agreement with those required for an equimolecular mixture of 4-diethylaminoethylamino-2:3:4':3'-quinoquinoline and 4-diethylaminoethoxy-2:3:4':3'-quinoquinoline (XC), which requires C, 76.5, H, 6.6, N, 14.2.



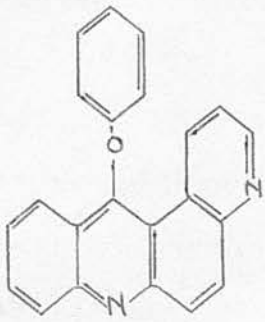


XC

Kermack and Hutchison (1946) had previously encountered difficulty in attempting to condense 2:5:8-trichloro-3:4:2':3'-pyridoacridine with 4-diethylamino-1-methylbutylamine in phenol in the same way. This gave a yellow crystalline base, which did not analyse for the desired compound, and it was formulated as a complex containing equimolecular proportions of 2:8-dichloro-5-(4-diethylamino-1-methylbutylamino)-3:4:2':3'-pyridoacridine (XCI) and the 5-phenoxy compound (XCII).



XCI

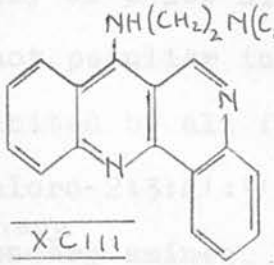


XCII

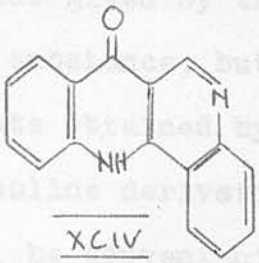
This type of formulation did not fit the analysis in the case of the quinoquinoline under discussion, however, ($C_{22}H_{24}N_4.C_{22}H_{14}ON_2.\frac{1}{2}H_2O$ requires C, 77.2, H, 5.85, N, 12.2.), but it is of interest that similar difficulties were encountered in the two series.

Another possibility that we considered was that the compound might be an equimolecular complex of the expected base (XCIII) and 2:3:4':3'-quino-

quinolo-4-one (XCIV).

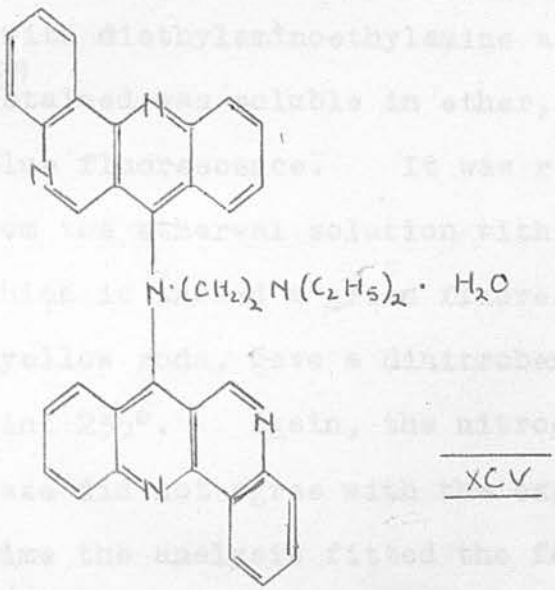


XCIII



XCIV

This would be isomeric with an alternative structure (XCV), where two chloro compounds have reacted with one molecule of side chain, and added on a molecule of water.



XCV

Both these representations ($C_{22}H_{24}N_4.C_{16}H_{10}ON_2$) require C, 77.3, H, 5.8, N, 14.2. The lack of close agreement of the figures found and those required for these two possibilities, tends to rule them out.

As will be seen from what follows, the anomalous result obtained here, and which consists essentially of a low nitrogen value given by the compound, is not peculiar to this one substance, but is exhibited by all five products obtained by treating 4-chloro-2:3:4':3'-quinoquinoline derivatives with ~~secondary~~ primary amines. It will be convenient to give the results of these other compounds, and then to survey them together in a later paragraph.

The preparation of 6'-methoxy-4-diethylaminoethylamino-2:3:4':3'-quinoquinoline was attempted by treating 6'-methoxy-4-chloro-2:3:4':3'-quinoquinoline with diethylaminoethylamine at 100°. The base (XCVI) obtained was soluble in ether, in which it showed a blue fluorescence. It was readily extracted from the ethereal solution with 5% acetic acid, in which it showed a green fluorescence. The base, yellow rods, gave a dinitrobenzoate, melting point 235°. Again, the nitrogen figure for this base did not agree with the expected value, but this time the analysis fitted the formula $C_{23}H_{25}O_2N_3$, which corresponds to the complete replacement of one -NH- by an oxygen atom. If such a simple replacement of -NH- by -O- had occurred, then this compound ought to be 4-diethylaminoethoxy-6'-methoxy-2:3:4':3'-quinoquinoline. This was prepared in the following way.

6'-Methoxy-4-diethylaminoethoxy-2:3:4':3'-quinoquinoline resulted when 6'-methoxy-4-chloro-2:3:4':3'-quinoquinoline and diethylaminoethanol were heated together in dry phenol. The product from this reaction was an oil, which could not be crystallised. It was soluble in ether, in which it showed a green fluorescence. It was not readily extracted from the ethereal solution with 5% acetic acid, a stronger concentration having to be used. The oily base gave a dinitrobenzoate melting at 103°. From a consideration of the two bases themselves, and also their dinitrobenzoates, it is obvious that the two compounds are chemically distinct. This makes it clear that the compound isolated when diethylaminoethylamine and 4-chloro-6'-methoxy-2:3:4':3'-quinoquinoline react together is not 6'-methoxy-4-diethylaminoethoxy-2:3:4':3'-quinoquinoline. The constitution of the base is still obscure.

The preparation of 6'-methoxy-4-(4-diethylamino-1-methylbutylamino)2:3:4':3'-quinoquinoline was attempted by heating a mixture of 6'-methoxy-4-chloro-2:3:4':3'-quinoquinoline and 2-amino-5-diethylaminopentane, in phenol. The reaction mixture was worked up as before, and the product crystallised as long yellow prisms from light petroleum.(60/80°).

Again, although the carbon and hydrogen fig-

ures agree with those required for the expected base, the nitrogen value was found to be low. The analytical results were in agreement with those required for an equimolecular mixture of 6'-methoxy-4-(4-diethylamino-1-methylbutylamino)-2:3:4':3'-quinoquinoline and 6'-methoxy-4-(4-diethylamino-1-methylbutoxy-)-2:3:4':3'-quinoquinoline (see experimental section.).

An attempt to prepare 6'-chloro-4-diethylaminoethylamino-2:3:4':3'-quinoquinoline was also made by heating 4:6'-dichloro-2:3:4':3'-quinoquinoline and diethylaminoethylamine together in dry phenol. The yellow, crystalline solid so obtained appeared to be homogeneous under the microscope, but it gave analytical results agreeing with the values calculated for an equimolecular mixture of 6'-chloro-4-diethylaminoethylamino-2:3:4':3'-quinoquinoline and 6'-chloro-4-diethylaminoethoxy-2:3:4':3'-quinoquinoline.

When 4:6'-dichloro-2:3:4':3'-quinoquinoline and 2-amino-5-diethylaminopentane were heated in dry phenol, a product, isolated as large yellow cubes, was obtained. The carbon and hydrogen analysis agreed with that expected of 6'-chloro-4-(4-diethylamino-1-methylbutylamino-)-2:3:4':3'-quinoquinoline, but again the nitrogen figure is low. The analysis would fit an equimolecular complex of the expected base and the corresponding dialkylamino-

ethoxy compound.

It will be seen that in every case the carbon and hydrogen figures agree with those calculated for the expected compound, but that invariably the nitrogen analysis is low. It seems scarcely possible that this is a coincidence, and it would appear that something unexpected is taking place. As the imino group is very nearly the same weight as one oxygen atom, it is difficult to avoid the conclusion that somehow -NH- is being replaced by -O-. In most cases, the replacement appears to be incomplete, as the analytical results agree best with those calculated for equimolecular proportions of the ether and the amino compound. The fact that the melting points of these products are not very sharp, (see experimental section), is in harmony with the view that they may be a mixture of two different compounds, even though they have resisted all attempts at separation by crystallisation and chromatography. That compound (XCVI), whose nitrogen content indicates a complete replacement of -NH- by -O-, is apparently different from the diethylaminoethoxy derivative, is very difficult to explain, and the whole question is being further investigated.

(e.) THE ATTEMPTED PREPARATION OF AMINES FROM 4-CHLORO-2:3:4':3'-QUINOQUINOLINE DERIVATIVES.

Although 4-aminoquinolines had previously been obtained only by the use of ammonia under pressure, Backeberg and Marais (1942) were able to prepare 4-amino compounds from the 4-chloro derivatives by passing a stream of ammonia through their solutions in phenol at 180°, a method which Albert, Brown and Duewell (1948) used to aminate 4-chlorobenzquinolines. This method is cumbersome on a large scale, particularly when it is important to use dry ammonia, and in the present instance recourse was at first made to a method described by Albert and Ritchie (1941), in which they aminate 5-chloroacridines and 5-chlorobenzacridines (which are 4-chloroquinolines) by ammonium carbonate in phenol at 120°. A.R. ammonium carbonate (said to be an equimolecular mixture of ammonium carbamate and ammonium bicarbonate) ensures a ready concentration of pure, dry ammonia without the difficulties which arise in the preparation of the gas. However, in our hands the method was not successful, in conformity with Albert, Brown and Duewell's observations that certain 4-chloroquinoline derivatives, such as those in the benzquinoline series, could not be aminated in this way, and we adopted the method of Backeberg and Marais.

The general procedure was to dissolve the chloro-compound in dry, freshly distilled phenol, which was then heated at 120° in an oil bath. Dry ammonia was passed through the solution for 2 hours, after which, the reaction mixture was basified with sodium hydroxide to yield a solid, which after separation was extracted with dilute acetic acid. On rendering alkaline, a base was precipitated which was purified by recrystallisation. The alkaline solution on standing yielded some 4-phenoxy compound.

The preparation of 6'-methoxy-4-amino-2:3:4':3' quinoquinoline was attempted in this way from the corresponding chloro compound. The product gave analytical data in agreement with the expected carbon and hydrogen figures, but the nitrogen result was low, ~~but~~ agreeing with that for an equimolecular amount of 6'-methoxy-4-amino-2:3:4':3'-quinoquinoline and 6'-methoxy-4-hydroxy-2:3:4':3'-quinoquinoline. The seemingly homogeneous compound reacted with methyl iodide in nitrobenzene to give 6'-methoxy-4-amino-2:3:4':3'-quinoquinoline monomethiodide. In this case the nitrogen figure agreed with that expected, which lends support to the idea that there was a mixture present, one constituent of which reacted more readily with methyl iodide than the other. The methiodide gave an anhydronium base on

treatment with alkali.

The synthesis of 4'-chloro-4-amino-2:3:4':3'-quinoquinoline was similarly attempted, but here again a product was obtained which gave analytical data agreeing with an equimolecular amount of 6'-chloro-4-amino-2:3:4':3'-quinoquinoline and 6'-chloro-4-hydroxy-2:3:4':3'-quinoquinoline. (see experimental section).

These results, obtained when a 4-chloro-2:3:-4':3'-quinoquinoline is treated with ammonia, seem similar to those obtained with ~~secondary~~ primary amines discussed in the previous section. The analytical figures show suitable agreement as far as carbon and hydrogen are concerned, but the nitrogen value is low, and in both cases they agree with those expected if equimolecular amounts of amino compound and quinoquinolone are present. In the case of these two compounds, it is easier to account for some of the oxy-derivative accompanying the amino compound, as traces of water in the phenol-ammonia reaction mixture would readily give rise tosome of the 4-hydroxyquinoquinoline, and an equimolecular complex might separate during the crystallisation process. If these are indeed mixtures or molecular complexes of amino and hydroxy 2:3:4':3'-quinoquinolines, they are very difficult to separate; an attempt to do so chromatographically failed.

This matter is still being investigated, but at present the constitution of these products must be left open until further evidence has accumulated.

EXPERIMENTAL

EXPERIMENTAL

DIETHYL ETHOXYMETHYLENEMALONATE.

Claisen, Ann., 1897, 297, 75.

Ber., 1893, 26, 2731.

Wheeler and Johns, Amer. Chem. J., 40, 233,(1908).

Fuson, Parham and Reed, J. Org. Chem., 1946, 11, 194.

The details of this method of preparation were kindly supplied by Imperial Chemical Industries Ltd. (Dyestuffs Division).

Diethyl malonate (240 c.c.), ethyl orthoformate (265 c.c.), acetic anhydride (305 c.c.) and powdered anhydrous zinc chloride (18 gm.) were heated together in a 2 litre three-necked flask, fitted with a thermometer and two reflux condensers, set in an oil bath. The reaction started at an internal temperature of 90-100°, after which the solution becomes violently agitated - the oil bath had to be removed on one occasion when the ebullition became too vigorous. After 15 -30 minutes, when the reaction had subsided, the condensers were removed, one being replaced by a stopper and the other by a fractionating column and condenser set for distillation. Heating was continued for ten hours (internal temp. 100-130°.), during which period ethyl acetate distilled off slowly. When cold,

the reaction mixture was filtered to remove zinc salts and the filtrate was fractionally distilled in a vacuum. The first fraction was a mixture of the volatile constituents - ethyl acetate, acetic anhydride, acetic acid and ethyl orthoformate, which came over at 60-80°/50 mm. The second fraction, distilling at 114-110°/19-13 mm ., consisted mainly of diethyl malonate, and the third fraction at 174°/9 mm. was diethyl ethoxymethylenemalonate.

A non-volatile residue is left in the flask, which is claimed to be 3:5-dicarbethoxy-6-ethoxy-α-pyrone. (I.C.I. Ltd., private communication.)

Yield 170 gm. (65% of theory.)

ETHYL β-ANILINO-α-CARBETHOXY-ACRYLATE.

Claisen, Ann., 1897, 297, 1.

Duffin and Kendall, J.C.S., 1948, 893.

Riegel et al., J.A.C.S., 1946, 1264.

Schofield and Simpson, J.C.S., 1946, 1033.

Diethyl ethoxymethylenemalonate (31 gm.) and freshly distilled aniline (13.9 gm.) were heated on a boiling water bath for 30 mins., during which time any ethanol formed was removed in vacuo. The product, a brown syrup, solidified on standing to a whitish solid, which was collected on a nutsche, washed with light petroleum (40/60°) and dried to give a buff-coloured solid, m.p. 40-43°. Crystallisation of this solid from light petroleum (40/60°) yielded colourless platelets, m.p. 46-48°, of ethyl β-anilino-α-carbethoxy-acrylate. Yield 33 gm. (88% of theory.)

Claisen obtained this acrylate in solid form and quotes the melting point as 50°. Schofield and Simpson, however, state that they were unable to obtain any crystalline material from the crude oily product. Duffin and Kendall also record a melting point of 50°, and Riegel et al. that of 49°.

ETHYL 4-HYDROXYQUINOLINE-3-CARBOXYLATE.

Schofield and Simpson, J.C.S., 1946, 1033.

Ethyl β-anilino-α-carbethoxy-acrylate (26.3 gm.) m.p. 46-48°, was added in small portions, and with efficient stirring, to liquid paraffin (10 parts) at 255-265°. After 20 min. heating, during which time sublimation occurred, the turbid solution was cooled, diluted with light petroleum (60/80°) and filtered. The solid was digested with boiling light petroleum (60/80°) to remove all traces of the mineral oil and dried. M.P. 272-4°. Yield 16 gm. (74% theory.) Crystallisation from ethanol gave a m.p. of 273-4°. (Schofield and Simpson found 275-6°.)

The ester is insoluble in aqueous sodium carbonate, sparingly soluble in ethanol and ethyl acetate and readily soluble in ether.

Attempts to cyclise ethyl β-anilino-α-carbethoxy-acrylate before purification gave low yields, and it was found that the combined liquid paraffin filtrate and light petroleum extracts deposited a white solid, (m.p. 110-2°) on standing. This compound when crystallised from light petroleum (60-80°) gave straw-coloured needles, m.p. 114-116°; 118° (Schofield and Simpson.). It was insoluble in hot sodium carbonate, cold sodium hydroxide and cold 2N-hydrochloric acid. From analysis, its empirical formula is found to be $C_{18}H_{18}O_3N_2$. (Schofield and Simpson.)

0.5 gm. of the compound was heated in boiling diphenyl under reflux for 30 mins. The solution was cooled and the diphenyl extracted with ether to leave a solid residue, which after washing with ether and drying melted at 315°.

This product on crystallisation from glacial acetic acid melted at 318°, and showed no depression in melting point when mixed with an authentic sample of the anilide of 4-hydroxyquinoline-3-carboxylic acid (prepared on page 136.).

From these facts, the compound melting at 118° was assumed to be ethyl β-anilino-α-phenylcarbamyl-acrylate, confirmed by comparison with the product prepared on the next page.

ETHYL β-ANILINO-α-PHENYLCARBAMYL-ACRYLATE.

Ethyl β-anilino-α-carbethoxy-acrylate (1.3 gm) m.p. 46-8°, was heated at 100° with an equimolecular amount of aniline for 1 hour, after which time it was found that the melt had solidified. M.P. 110-114°.

The product was crystallised from light petroleum (60-80°), giving straw-coloured, needle-shaped crystals of m.p. 116-118°. Yield 1.3 gm. (84% theory.) Ethyl β-anilino-α-phenylcarbamyl-acrylate thus prepared showed no depression in melting point when mixed with a sample of the by-product $C_{18}H_{18}O_3N_2$ mentioned in the previous experiment.

4-HYDROXYQUINOLINE-3-CARBOXYLIC ACID.

Schofield and Simpson, J.C.S., 1946, 1033.
Duffin and Kendall, ibid., 1948, 893.

Ethyl 4-hydroxyquinoline-3-carboxylate (10 gm.) m.p. 273-4° was hydrolysed by heating with 5% aqueous sodium hydroxide (40 c.c.) on a steam bath for 40 minutes. As hydrolysis occurred, the solid slowly went into solution to give a clear light brown liquid; this was treated with charcoal, and filtered hot. The cold filtrate was acidified with dilute acetic acid, whereupon a voluminous white precipitate formed, which was filtered, washed with water and dried. The product melted at 263-265° with effervescence.

The acid was crystallised from nitrobenzene and had m.p. 268-70°, with effervescence; 269-70° (Schofield and Simpson.); 270° (Duffin and ~~Taylor~~ KENDALL .). Yield 8 gm. (97% theory.)

4-Hydroxyquinoline-3-carboxylic acid is soluble in aqueous sodium carbonate and bicarbonate, and sparingly soluble in water. It gives no colour with ferric chloride solution.

It was found that if unpurified ethyl 4-hydroxyquinoline-3-carboxylate prepared from crude ethyl β-anilino-α-carbethoxy-acrylate is used for this hydrolysis, then the 5% aqueous sodium hydroxide solution deposits a solid on cooling. Furthermore, if the hot aqueous sodium hydroxide solution

is acidified with dilute acetic acid, the product is only partially soluble in sodium carbonate. In this way 4-hydroxyquinoline-3-carboxylic acid, the soluble portion, may be separated from the impurity. The residue is found to have a melting point of 314-16°. It is insoluble in aqueous sodium carbonate, bicarbonate or hydrochloric acid, but soluble in hot aqueous sodium hydroxide solution, from which a colourless sodium salt separates on cooling. The substance was crystallised from glacial acetic acid to give colourless plates of m.p. 318-20°; 318° (Schofield and Simpson.). Its empirical formula was found to be either $C_{16}H_{12}O_2N_2$ or $C_{15}H_{12}O_2N_2$ (Schofield and Simpson.).

The solid (1 gm.) was treated with 5% sulphuric acid (30 c.c.) and refluxed for 3½ hours: after 1 hour the solution was found to give a positive diazo test. On cooling and diluting with water a solid separated, which was filtered, washed with water, and dried. M.P. 265-67° with effervescence.

The solid is readily soluble in aqueous sodium carbonate and bicarbonate, but is insoluble in acid solution; a small amount mixed with 4-hydroxyquinoline-3-carboxylic acid melted at 265-67°, showing no depression.

The original compound would from this appear to be the anilide of 4-hydroxyquinoline-3-carboxylic

acid, the hydrolysis of which would lead to aniline and 4-hydroxyquinoline-3-carboxylic acid. The identity of the compound was further confirmed by comparison with an authentic specimen. (see next experiment.)

4-HYDROXY-3-PHENYLCARBAMYLQUINOLINE.

Ethyl 4-hydroxyquinoline-3-carboxylate (1gm.) was refluxed with aniline (1 gm.) for five hours. On cooling, the solution deposited shining white plates, which were filtered, washed with ethanol, and dried. M.P. 316-18°. Yield 1.2 gm. (89% theory)

A small amount of this solid mixed with a portion of the by-product of the previous experiment melted at 316-18°, showing no depression.

4-Hydroxy-3-phenylcarbamylquinoline gives no colour with an aqueous solution of ferric chloride; it is insoluble in sodium carbonate, and hydrochloric acid, but soluble in warm aqueous sodium hydroxide solution. It may be recovered unchanged by prolonged boiling in 10% aqueous sodium hydroxide.

As mentioned previously (p.132), the anilide of 4-hydroxyquinoline-3-carboxylic acid may also be prepared by cyclising ethyl β-anilino-α-phenylcarbamyl-acrylate in boiling diphenyl solution.

4-HYDROXYQUINOLINE:

Duffin and Kendall, J.C.S., 1948, 893.

Two methods of decarboxylating the acid were used.

(1.) 4-Hydroxyquinoline-3-carboxylic acid, (2.5 gm.) m.p. 268-70°, was placed in a 25 c.c. beaker and heated gently over a small flame or immersed in a metal bath. A thermometer, used as a stirrer, registered the temperature which was kept as near 270° as possible. Heating was continued until no further effervescence occurred. The melt was cooled, dissolved in ethanol (25 c.c.), treated with decolourising charcoal, and filtered hot. The filtrate was evaporated to a small volume on the water bath and allowed to cool, when 4-hydroxyquinoline separated from the concentrate in the form of white needles, m.p. 200-201°; 201 (Duffin and Kendall.). Yield 0.86 gm. (45% theory.) The average yield from a large number of experiments was 52%.

(2.) 4-Hydroxyquinoline-3-carboxylic acid (2.5 gm.) was also decarboxylated by adding to liquid paraffin (10 parts) and heating at 270-300° until all the acid dissolved (about 20 mins.). The cold viscous liquid was thinned with light petroleum (100/120°) and filtered from the separated solid. After crystallisation from ethanol the 4-hydroxy-

quinoline melted at 200-201°. Yield 0.8 gm. (42% of theory.)

4-Hydroxyquinoline is very soluble in ethanol and water, which solutions impart a red colour when a drop of aqueous ferric chloride solution is added to them,.

4-CHLOROQUINOLINE.

Riegel et al., J.A.C.S., 1946, 68, 1264.

4-Hydroxyquinoline (7.2 gm.) was added in small portions to phosphorus oxychloride (5 gm.). The reaction mixture warmed up considerably during the addition, and had to be cooled by immersion in cold water. The mixture was raised slowly to boiling point and refluxed for three hours, after which time the solid had dissolved completely, leaving a clear yellow solution. When cold, the liquid was poured slowly and with vigorous stirring, on to crushed ice to decompose the residual phosphorus oxychloride. The yellow solution thus formed was treated with decolourising charcoal and filtered. The filtrate, on rendering alkaline with dilute ammonium hydroxide, gave a buff-coloured oil which soon solidified on standing. (During basification, the temperature of the solution was maintained below 20° by an ice-salt freezing mixture.) The precipitate was filtered off, washed with ice water, and dried in a vacuum desiccator over potassium hydroxide.

Yield 6.1 gm. (75% theory.) M.P. 28-30°; 31° (Meisenheimer).

4-Chloroquinoline was reported to be an oil by Riegel et al.

4-o-AMINOPHENYLAMINOQUINOLINE.

cf. Kermack and Smith, J.C.S., 1930, 1999.

4-Chloroquinoline (3.2 gm.) and o-phenylene-diamine (2.1 gm.) were heated together at 140° in an oil bath under a pressure of 20-30 mm. After 10-20 mins. a violent reaction occurred, and the solution set to a brittle resin. The solid was extracted with boiling dilute hydrochloric acid (10%), the solution treated with charcoal and filtered hot. The filtrate on cooling, deposited a greyish-white mass of crystals, m.p. 285-90°.

The solid hydrochloride was dissolved in hot water and the solution treated with charcoal and filtered. The hot aqueous filtrate when basified with dilute NaOH (2N) liberated the base, which separated in straw-coloured prisms, m.p. 150-160°. Yield 3.5 gm. (76% theory.) On crystallisation from a mixture of benzene and light petroleum (40-60°) the melting point was raised to 165-6°.

Found: C, 76.4; H, 5.4; N, 17.4.

$C_{15}H_{13}N_3$ requires C, 76.6; H, 5.5; N, 17.8.

4-o-aminophenylaminoquinoline is soluble in dilute mineral acids, from which it may be precipitated by alkali. It dissolves readily in benzene and ethanol, but is almost insoluble in either water or light petroleum.

4-(BENZTRIAZOLYL-1')QUINOLINE.

cf. Kermack and Smith, J.C.S., 1930, 1999.

4-o-Aminophenylaminoquinoline (3 gm.) was dissolved in 3% hydrochloric acid (500 c.c.) and cooled to 5° by an ice-salt freezing mixture. A solution of sodium nitrite (0.8 gm.) in water (10 c.c.) was slowly added with constant stirring, until an excess of nitrite was present, as shown by reaction to starch iodide paper. The voluminous white precipitate of the hydrochloride which separated was filtered, dissolved in boiling water, and the base precipitated by the cautious addition of alkali to the hot solution. After cooling, the base separated, and was filtered, washed with water and dried. On crystallising from hot ethanol, it separated in slender white prisms which softened at 285° and melted at 293-4°. Yield 2.2 gm. (70% of theory.)

Found: C, 73.0; H, 4.2; N, 23.0.

$C_{15}H_{10}N_4$ requires C, 73.2; H, 4.1; N, 22.8.

4-(Benztriazolyl-1')quinoline is soluble in dilute acetic, nitric, hydrochloric and sulphuric acids, fairly soluble in ethanol but insoluble in water and benzene. It dissolves readily in cold concentrated sulphuric acid to give a solution which on heating turns yellow and exhibits a violet fluorescence in the arc light.

2:3-BENZ-γ-CARBOLINE.

cf. Kermack and Smith, J.C.S., 1930, 1999.

4-(Benztriazolyl-1')quinoline (10 gm.), dried over KOH in a vacuum desiccator for 48 hours, was heated in syrupy phosphoric acid (15 c.c.) until the evolution of nitrogen ceased. The reddish-brown solution was diluted with a large volume of water and neutralised with ammonium hydroxide. The base separated as a greyish-white flocculent precipitate which was filtered, washed and dried.

M.P. 337-40°, with sublimation. Yield 7.7 gm.

2:3-Benz-γ-carboline was purified by crystallisation from aqueous methanol and subsequent sublimation in vacuo. It was then recrystallised from aqueous methanol to give irregular, colourless prisms, m.p. 342° with sublimation. Yield 7 gm. (77% of theory.)

Found: C, 82.3; H, 4.9; N, 12.55.

$C_{15}H_{10}N_2$ requires C, 82.55; H, 4.6; N, 12.8.

This compound is insoluble in water, benzene and ether, sparingly soluble in ethanol, and still more soluble in methanol and pyridine. It dissolves readily in hot, dilute HCl to give a clear solution, which on cooling deposits white crystals of the hydrochloride. (Needles, m.p. 328-30°.) It is sparingly soluble in concentrated nitric acid, but easily dissolves on warming to yield a pale yellow solution, which when cold deposits a yellow nitrate,

m.p. >300°. The base exhibits a violet fluorescence under the arc lamp in all solvents, except in concentrated sulphuric acid, though the crude material showed a marked fluorescence in the cold.

2:3-BENZ -γ- CARBOLINE METHIODIDE.

2:3-Benz-γ-carboline (0.54 gm.) was dissolved in nitrobenzene (20 c.c.) with warming on the water-bath. Excess methyl iodode (0.4 gm.) was added and the mixture heated at 50-60° for 45 minutes, and allowed to stand overnight. The reaction mixture was heated at 50-60° for a further 30 minutes and left to stand at room temperature over the weekend, when a crop of long needle-shaped crystals deposited. These were filtered, washed with ether and dried. M.P. 285-300°. Yield 0.5 gm. A further crop was obtained by diluting the nitrobenzene filtrate with light petroleum (80-100°). Yield 0.2 gm. M.P. 297°.

The methiodide was crystallised from methanol containing a trace of sodium thiosulphate (2N) as the crystals were found to turn black on standing in the air. The colour may also be discharged by washing with sodium thiosulphate. Yield 0.64 gm. (72% of theory.)

Found: C, 53.4; H, 3.4; N, 7.5.

$C_{16}H_{13}N_2I$ requires C, 33.3; H, 3.6; N, 7.8.

When a trace of iodine dissolved in ethanol is added to the alcoholic solution of the methiodide, a dark red colour immediately develops, which deepens to black on standing. On adding dilute ammonium hydroxide to an aqueous solution of the methiodide, the anhydronium base precipitates as a yellow solid.

4-METHYL-2:3-BENZ-γ-ISOCARBOLINE.

A solution of 2:3-benz-γ-carboline methiodide (0.5 gm.) in hot water (10 c.c.) was rendered alkaline with ammonium hydroxide; the yellow precipitate which separated was filtered, washed and crystallised from dry benzene, from which it was obtained as clear, yellow prisms. On drying in a vacuum desiccator over P_2O_5, the compound was found to melt at 195° with frothing. Yield 0.2 gm. (63% of theory.)

Found: C, 75.75; H, 5.5.

$C_{16}H_{12}N_2.H_2O$ requires C, 76.8; H, 5.6.

On drying the material in vacuo at 80° over P_2O_5 for 4 hours, a yellow amorphous powder was formed, which still melted at 195°, but without frothing. The powder was then analysed.

Found: C, 82.8; H, 5.0; N, 11.7.

$C_{16}H_{12}N_2$ requires C, 82.75; H, 5.2; N, 12.1.

4-Methyl-2:3-benz-γ-isocarboline was readily soluble in ethanol, methanol and benzene. It imparts an alkaline reaction to water.

4-DIETHYLAMINOETHYL-2:3-BENZ-γ-ISOCARBOLINE.

Diethylaminoethyl chloride, liberated from its hydrochloride by basification with sodium hydroxide, was extracted with ether, and the ethereal solution dried over anhydrous potassium carbonate. After filtration from the drying agent, the ether was removed *in vacuo* and the remaining base distilled; the fraction coming over at 49-50°/16 mm. was collected.

2:3-Benz-γ-carboline (0.54 gm.) was dissolved in nitrobenzene (100 c.c.) and an excess of diethylaminoethyl chloride (0.5 gm.). The solution was heated on a boiling water bath under reflux for nine hours, and allowed to stand at room temperature for a week (convenience). The nitrobenzene solution was filtered from a small white sediment which had separated, diluted with light petroleum (100-120°), and the resulting brown precipitate filtered off at the pump. The product was washed with ether, dissolved in water and the aqueous solution basified with ammonia. The resulting yellow base had a m.p. of 75-85°, which on crystallisation from aqueous ethanol rose to 84-85°. On drying in a vacuum desiccator over calcium chloride, the yellow needles changed to a highly viscous liquid. When an analytical specimen of the crystals was dried over P_2O_5 at 80° under vacuum, the loss of weight was 5.07%.

The resulting, viscous liquid gave the following results on analysis:

Found: C, 74.3; H, 7.35; N, 12.2.

$C_{21}H_{23}N_3.1\frac{1}{2}H_2O$ requires C, 74.2; H, 7.5; N, 12.4.

From these figures it appears that the liquid is the monohydrate of the expected base, and that the crystals (m.p. 84-86°) represent a dihydrate. The calculated figure for the loss of one molecule of water from the dihydrate to the monohydrate being 5.09%.

4-Diethylaminoethyl-2:3-benz-γ-isocarboline dihydrate is soluble in hot ethanol, benzene and light petroleum, less soluble in water and insoluble in aqueous sodium hydroxide. It is not markedly fluorescent in any of its solutions.

The small white sediment filtered from the nitrobenzene reaction mixture was found to have a m.p. of 350° crude. It is very soluble in water, but its aqueous solution gives no precipitate on basification with ammonia. Potassium iodide added to its aqueous solution brings down a precipitate melting above 300°. The product was assumed to be tetraethylpiperazinium dichloride, formed by the interaction of two molecules of amine, since it is identical with the compound which separates in leaflets when diethylaminoethyl chloride is allowed to stand in ethanol for a prolonged period. (cf. H.King, J.C.S., 1928, 2436.)

1-DIETHYLAMINOETHYL-2:3-BENZ-γ-CARBOLINE.

cf. Dewar, J.C.S., 1944, 619.

Diethylaminoethyl chloride was isolated from its hydrochloride by basification with NaOH, extracted with ether and purified by distillation in vacuo.

2:3-Benz-γ-carboline (1.09 gm.), diethylaminoethyl chloride (1.01 gm.) and finely powdered sodamide (1.95 gm.) were mixed together with toluene (10 c.c.) and heated on an oil bath at 70° for 30 minutes. The temperature was then raised to 115° for 30 minutes and refluxed at 110° for 4 hours. After cooling, water was added, and a small amount of unchanged benzcarboline removed by filtration. The toluene layer was separated in a separating funnel and extracted 6 times with 10 c.c. portions of acetid acid (5%). The combined acid extracts were basified with ammonium hydroxide and the resulting oily precipitate extracted with ether. The ethereal solution was dried over anhydrous potassium carbonate for three hours, after which it was filtered and evaporated to a small volume. Fine crystals separated, m.p. 97-99°, which were recrystallised from aqueous ethanol, m.p. 103-4°. Yield 0.96 gm. (60% of theory.)

Found: C, 79.6; H, 7.1; N, 13.2.

$C_{21}H_{23}N_3$ requires C, 79.5; H, 7.25; N, 13.25.

1-Diethylaminoethyl-2:3-benz-γ-carboline is soluble in benzene and acetone, and its solution in dilute acetic acid shows a sky blue fluorescence.

4-DIETHYLAMINOETHYL-2:3-BENZ-γ-CARBOLINE DIMETHIODIDE.

4-Diethylaminoethyl-2:3-benz-γ-isocarboline dihydrate (0.53 gm.) was dissolved in nitrobenzene (10 c.c.) with warming. Methyl iodide (0.24 gm.) was then added, and the mixture heated under reflux at 60° for 30 minutes. Needle-shaped crystals separated from the clear solution almost immediately, which were filtered, washed with ether and dried. M.P. 254-6°. The base was crystallised from boiling water, giving white, feathery needles of m.p. 263-4°. Yield 0.69 gm.

Found: C, 45.75; H, 4.65; N, 6.6.

$C_{21}H_{23}N_3.2CH_3I$ requires C, 45.9; H, 4.8; N, 6.9.

4-Diethylaminoethyl-2:3-benz-γ-carboline-dimethiodide is soluble in water, in which solution it shows no fluorescence. Its aqueous solution gives no precipitate with ammonium or sodium hydroxide, indicating that an anhydronium base is not formed. The methiodide is soluble in dilute hydrochloric acid.

-2:3-

1-DIETHYLAMINOETHYLAMINOBENZ-γ-CARBOLINE METHIODIDE.

4-Methyl-2:3-benz-γ-isocarboline (0.5 gm.) and diethylaminoethyl chloride (0. gm.) were refluxed together in nitrobenzene (20 c.c.) for 5½ hours, and allowed to stand at room temperature overnight. The mixture was refluxed a further 3 hours and cooled. A white solid was filtered off which was identical with 1:4-tetraethylpiperazinium dichloride, m.p. c.350°. The nitrobenzene filtrate was diluted with light petroleum (80-100°) and allowed to stand for one hour. The separated solid was filtered, washed with ether and dried. M.P. 70-90°. This was dissolved in water, and a saturated solution of potassium iodide was added. Crystals separated immediately and were filtered off. M.P. 220°. 1-Diethylaminoethylamino-2:3-benz-γ-carboline methiodide was crystallised from aqueous alcohol. M.P. 225°.

Only a small quantity of this material was isolated, and so without being analysed, the compound was treated with methyl iodide in nitrobenzene at 100°. The product which separated was removed by filtration. It melted at 270-74°, and was identical in all respects with 1-diethylaminoethyl-2:3-benz-γ-carboline dimethiodide (m.p. 276-8°), whose melting point it did not depress.

ETHYL α-CARBETHOXY-β-(p-ANISIDINO)-ACRYLATE.

Price and Roberts, J.A.C.S., 1946, 68, 1204.
Schofield and Simpson, J.C.S., 1946, 1033.
Duffin and ~~Taylor~~ Kendall, ibid., 1948, 893.

A mixture of finely ground p-anisidine (31 gm.) and diethyl ethoxymethylene malonate (54 gm.) were heated on a water bath for 30 minutes, the ethanol formed being removed from the system by distillation in vacuo. The product, a dark oil, solidified partially on standing, forming large, opaque crystals about 1 cm. long embedded in a syrupy matrix. These were collected on a nutsche, washed with light petroleum (40/60°), air dried and found to melt at 38-9°. The product was difficult to purify as it tended to separate as an oil from either light petroleum or ether. Ethyl α-carbethoxy-β-(p-anisidino)-acrylate was eventually crystallised from light petroleum (80/100°), giving large dog-tooth prisms melting at 38-40°. Yield 40.6 gm. (55% theory.)

Found: C, 61.1; H, 6.2; N, 4.9.

$C_{15}H_{19}O_5N$ requires C, 61.4; H, 6.5; N, 4.8.

Schofield and Simpson reported that they were unable to obtain any crystalline material from the crude oily product, and Price and Roberts recorded a melting point of between -12° and -15°, obtained by placing a thermometer in the melting crystals. Presumably the products obtained by these authors were ethyl α-carbethoxy-β-(p-anisidino)-acrylate in a somewhat impure form.

ETHYL 4-HYDROXY-6-METHOXYQUINOLINE -3- CARBOXYLATE.

cf. Schofield and Simpson, J.C.S., 1946, 1033.

Price and Roberts, J.A.C.S., 1946, 68, 1204.

Ethyl α-carbethoxy-β-(p-anisidino)-acrylate (38 gm.) was added to boiling diphenyl (500 c.c.), and the solution was heated under reflux for 30 mins., allowed to cool, and diluted with 500 c.c. of petroleum ether (80-100°). The insoluble, buff-coloured residue was separated by filtration and washed with light petroleum (80-100°) and ethyl ether. When dry, the product melted at 270-5° and weighed 25.6 gm. (80% theory.) On crystallisation from aqueous ethanol, the melting point was raised to 278-80°; 280-1° (Schofield and Simpson); 274-7° (Price and Roberts).

Ethyl 4-hydroxy-6-methoxyquinoline-3-carboxylate is insoluble in water, light petroleum and ether, but soluble in ethanol, glacial acetic acid and hydrochloric acid solution.

No by-products were obtained in this experiment even when using crude, unpurified ethyl α-carbethoxy-β-(p-anisidino)-acrylate. (cf. Schofield and Simpson).

4-HYDROXY-6-METHOXYQUINOLINE-3-CARBOXYLIC ACID.

Schofield and Simpson, J.C.S., 1946, 1033.

Price and Roberts, J.A.C.S., 1946, 68, 1204.

Hydrolysis of ethyl 4-hydroxy-6-methoxyquinoline-3-carboxylate (16 gm.) was effected by heating the ester at 90° with 5% aqueous sodium hydroxide (20 c.c.). After one hour the solution was treated with decolourising charcoal, and filtered hot through a fluted filter paper. 4-Hydroxy-6-methoxyquinoline -3-carboxylic acid, obtained by acidifying the filtrate with dilute acetic acid, melted at 270° with decomposition. On crystallisation from acetic acid, in which it is only sparingly soluble, the acid separated in feathery needles, and melted with effervescence at 276-8°; 278-9°(Schofield and Simpson.); 271-2° (Price and Roberts.) Yield 13.6 gm. (95% theory).

The acid is readily soluble in sodium carbonate solution, from which it may be precipitated by dilute acids. When a drop of ferric chloride solution was added to an aqueous solution of the compound, a pink colour developed.

4-HYDROXY-6-METHOXYQUINOLINE.

cf. Price and Roberts, J.A.C.S., 1946, 68, 1204.

4-Hydroxy-6-methoxyquinoline-3-carboxylic acid (7.2 gm.) was decarboxylated by placing it in a small beaker immersed in a metal bath, and heating at 270-80° till the effervescence ceased. The product was dissolved in hot water (20 c.c.), treated with charcoal and filtered. 4-Hydroxy-6-methoxyquinoline separated from the filtrate in the form of white needles, m.p. 236-8°. On recrystallisation from water, the compound melted at 239-40°; 239-40° (Price and Roberts.) Yield 4.5 gm. (76% theory.)

4-Hydroxy-6-methoxyquinoline is very soluble in hot water and ethanol; it is insoluble in cold acid and alkali. A drop of ferric chloride solution imparts a deep red colour to its aqueous solution.

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4-CHLORO-6-METHOXYQUINOLINE.

cf. Price and Roberts, J.A.C.S., 1946, 68, 1204.

4-Hydroxy-6-methoxyquinoline (9 gm.) was converted into the 4-chloro compound by gently refluxing with phosphorus oxychloride (20 c.c.) and phosphorus pentachloride (5.2 gm.) for six hours. When cold, the solution was poured on to crushed ice, and after treatment with charcoal, was basified with ammonium hydroxide. 4-Chloro-6-methoxyquinoline separated as a buff-coloured precipitate, melting at 74-6°; 74-5° (Price and Roberts.) Yield 8 gm. (81% theory.).

In order to prepare several grams of 4-chloro-6-methoxyquinoline, relatively quickly and without isolation at every stage, it was decided to carry out a 'continuous' experiment as described by Price and Roberts for the preparation of 4:7-dichloroquinoline.

p-Anisidine (16 gm.) and diethyl ethoxymethylene malonate (28 gm.) were dissolved in a mixture of diphenyl (100gm.) and diphenyl ether (150 gm.), which was raised slowly to boiling point and boiled in an open vessel to allow the ethanol formed to escape. After 30 minutes, the cyclisation mixture was cooled to 90°, and 10% aqueous sodium hydroxide

(100 c.c.) added, cautiously and with stirring. A reflux condenser was attached to the flask, and the heterogeneous mixture was boiled vigorously for a further 30 minutes until the solid material had disappeared. When cold, the aqueous layer was separated, acidified with acetic acid, and the precipitated acid was collected on a filter, washed with water and sucked as dry as possible. A small sample, dried on a piece of porous plate, melted at 270-5°, and was soluble in aqueous sodium carbonate solution. The filter cake was recombined with the diphenyl/diphenyl ether layer, which had been washed with water to remove any adherent sodium hydroxide. Fresh solvent (40 c.c.) was added, and the mixture was raised to boiling point cautiously, allowing the occluded water time to escape smoothly. As decarboxylation proceeded, solid went into solution and after one hour's boiling, the reaction was apparently complete. The reaction mixture was allowed to cool to room temperature and phosphorus oxychloride (35 c.c.) was added carefully, though practically no heat was evolved. After heating at 135-40° for an hour longer, the black solution was cooled, diluted with ether, and extracted with water. Six one hundred c.c. portions were used. Ice was added to the combined aqueous extracts, which on neutralisation with dilute sodium hydroxide yielded a black tar.

This was washed with water, acetone and ethanol to give eventually a small amount of brown solid melting at 230-5°, and which gave a positive halogen test. The solid material was dissolved in dilute acetic acid, treated with charcoal, filtered and reprecipitated with dilute ammonium hydroxide. After this purification process, the substance melted at 236-8° and gave no positive halogen test. A small portion mixed with a sample of 4-hydroxy-6-methoxyquinoline (m.p. 238-40°) melted at 236-8°, showing no depression. The small residue was therefore considered to be 4-hydroxy-6-methoxyquinoline, which had either escaped the action of phosphorus oxychloride, or had been regenerated by the hydrolysis of 4-chloro-6-methoxyquinoline.

From this and other similar experiments, it was found best to interrupt the 'continuous' experiment before the treatment with phosphorus oxychloride, and to isolate the 4-hydroxy-6-methoxyquinoline by precipitation from the diphenyl/diphenyl ether mixture with light petroleum. The hydroxy compound was then converted to the 4-chloro-6-methoxyquinoline by treatment with phosphorus oxychloride and pentachloride in the usual way.

An experiment of this type showed that from 10gm. of p-anisidine, 11.6 gm. of 4-chloro-6-methoxyquinoline was obtained, corresponding to an overall yield of 74% of chloro compound on the p-anisidine used.

6-METHOXY-4-o-AMINOPHENYLAMINOQUINOLINE.

cf. Kermack and Smith, J.C.S., 1930, 1999.

When 4-chloro-6-methoxyquinoline (3.9 gm.) and o-phenylene diamine (2.16 gm.) were condensed together at 140° under reduced pressure, a vigorous reaction took place and the liquid frothed up, to set almost immediately to a hard, porous mass. Heating was stopped, and the solid was extracted with hot, dilute hydrochloric acid (20 c.c.). After charcoaling and filtering the solution hot, the solution was made alkaline with ammonium hydroxide and the resulting yellow precipitate collected on a nutsche, washed with water, and dried. M.P. 165-8°.
On crystallisation from benzene, the base separated as colourless, rectangular plates, melting sharply at 192°. Yield 2.5 gm. (47% theory.)

Found: C, 72.3; H, 5.5; N, 15.7.

$C_{16}H_{15}ON_3$ requires C, 72.5; H, 5.7; N, 15.85.

6-Methoxy 4-o-aminophenylaminoquinoline is soluble in most dilute mineral acids, and in concentrated sulphuric acid in which it showed no fluorescence. It is sparingly soluble in benzene, soluble in ethanol, but insoluble in water.

6-METHOXY(4-BENZTRIAZOLYL-1')QUINOLINE.

cf, Kermack and Smith, J.C.S., 1930, 1999.

To a solution of 6-methoxy 4-o-aminophenylaminoquinoline (3.5 gm.) in 3% hydrochloric acid (100 c.c.), a solution of sodium nitrite (1.15 gm.) in water (5 c.c.) was added with stirring at 5°, till a slight excess was present. The solution was allowed to stand at room temperature for 2 hours, after which time the voluminous precipitate of the hydrochloride was filtered off, washed and dried. M.P. 160-180°. The hydrochloride was dissolved in boiling water and converted to the base by rendering alkaline with ammonium hydroxide; m.p. 124-5°. After several crystallisations from light petroleum (80/100°) 6-methoxy(4-benztriazolyl-1')quinoline melted at 129-30°. Yield 2.5 gm. (52% theory.)

Found: C, 70.2; H, 4.2; N, 20.5.

$C_{16}H_{12}ON_4$ requires C, 69.6; H, 4.3; N, 20.3.

The base is soluble in ethanol, methanol and petroleum ether, and very soluble in benzene. It is insoluble in alkali but soluble in all mineral acids. The yellow solution in concentrated sulphuric acid effervesces and turns brownish-red on heating.

15-METHOXY-2:3-BENZ-γ-CARBOLINE.

cf. Kermack and Smith, J.C.S., 1930, 1999.

6-Methoxy-4-(benztriazolyl-1')quinoline (5 gm.), dried over potassium hydroxide in a vacuum desiccator for 48 hours, was heated in syrupy phosphoric acid (20 c.c.) until the evolution of nitrogen ceased. The reddish-brown solution was poured into a large excess of water and neutralised with ammonium hydroxide. A yellow, gelatinous precipitate separated, which was collected at the pump and washed with water. On allowing to dry in the air, the product turned black and shrank to a hard, brittle cake, m.p. above 400°. The solid immediately turned white on addition to dilute (2N) hydrochloric acid, in which it dissolved in the hot and deposited a white hydrochloride on cooling. M.P. 310°.

Found: C, 57.5; H, 4.8.

$C_{16}H_{12}ON_2.2HCl.\frac{3}{4}H_2O$ requires C, 57.4; H, 4.65.

The white base, when regenerated from the hot aqueous solution of the hydrochloride by neutralisation with ammonium hydroxide, melted at 315°.

Found: C, 77.0; H, 4.8; N, 11.1.

$C_{16}H_{12}ON_2$ requires C, 77.4; H, 4.8; N, 11.3.

15-Methoxy-2:3-benz-γ-carboline is sparingly soluble in ethanol and methanol, and soluble in hot, dilute mineral acids. It exhibits no fluorescence

in concentrated sulphuric acid.

On one occasion when this preparation was attempted, the product isolated from the neutralised phosphoric acid solution was found to melt at 196-8°. On admixture with a sample of 6-methoxy-4-o-aminophenylaminoquinoline (m.p. 192°), a depression of 10° resulted. The product when crystallised from ethanol gave a white crystalline solid, melting at 220°. On dissolving in hot, dilute hydrochloric acid, a pale yellow crystalline hydrochloride separated on cooling. The salt melted at 215°.

The base proved to be identical with 6-methoxy-4-anilinoquinoline, obtained by decarboxylating 6-methoxy-4-anilinoquinoline-3-carboxylic acid, and this was confirmed by analysis.

Found: C, 76.4; H, 5.8.

$C_{16}H_{14}ON_2$ requires C, 75.8; H, 5.6.

The isolation of this compound is discussed in the theoretical section.

ETHYL α-CARBETHOXY-β-(p-CHLOROANILINO)-ACRYLATE.

cf. Riegel et al., J.A.C.S., 1946, 68, 1264.
Tarbell, ibid., 1946, 68, 1277.
Duffin and Kendall, J.C.S., 1948, 893.

When p-chloroaniline (19.12 gm.) and diethyl-ethoxymethylene malonate (32.4 gm.) were heated together for one hour on the water bath under reduced pressure, an oil formed which on cooling set to a solid mass. After crystallisation from light petroleum (40/60°), the product weighed 43 gm. (77% of theory) and melted at 82-3°; 82° (Duffin and Kendall); 82-3° (Riegel et al.); 81-2° (Tarbell).

Ethyl α-carbethoxy-β-(p-chloroanilino)-acrylate is a white, crystalline compound which is soluble in alcohol and light petroleum, but insoluble in water.

ETHYL 6-CHLORO-4-HYDROXYQUINOLINE-3-CARBOXYLATE.

cf. Duffin and Kendall, J.C.S., 1948, 893.
Riegel *et al.*, J.A.C.S., 1946, 68, 1264.
Tarbell, *ibid.*, 1946, 68, 1278.

Ethyl α-carbethoxy-β-(p-chloroanilino)-acrylate (30 gm.) was cyclised to the hydroxy ester by heating in a mixture of refluxing diphenyl (150 gm.) and diphenyl ether (130 gm.). After 40 minutes, the clear solution was cooled, diluted with light petroleum (80/100°), and the insoluble material filtered off. The ethyl 6-chloro-4-hydroxyquinoline-3-carboxylate was then well washed with light petroleum (80/100°) to remove all traces of solvent and dried at 80° in the oven. It melted at 310° after crystallisation from nitrobenzene; above 280° (Riegel); 293° (Duffin and Kendall); 303-5° (Tarbell). Yield 16.5 gm. (65% of theory.)

The compound is soluble in nitrobenzene and pyridine; it is sparingly soluble in glacial acetic acid. The melting point was found to vary slightly with the rate of heating, which may account for the divergent values recorded in the literature, slow heating resulting in a somewhat lower value.

6-CHLORO-4-HYDROXYQUINOLINE-3-CARBOXYLIC ACID.

Ethyl 6-chloro-4-hydroxyquinoline-3-carboxylate (16 gm.) was hydrolysed to the corresponding acid by warming in the water bath with 10% sodium hydroxide (160 c.c.). The solid material gradually went into solution to give a pale yellow liquid which, after heating for 1½ hours, was treated with decolourising charcoal and filtered hot. The filtrate after basification with ammonium hydroxide yielded 6-chloro-4-hydroxyquinoline-3-carboxylic acid as a white powder melting at 260-2°. On crystallisation from ethanol the acid was found to soften at 260-1°, and melt with frothing at 278-9°; 261° (Riegel et al.); 250° (Tarbell); 261° (Duffin and Kendall).
Yield 12.8 gm. (90% of theory.)
Found: C, 53.7; H, 3.0; N, 6.4.
$C_{10}H_6O_3NCl$ requires C, 53.7; H, 2.7; N, 6.3.

The hydroxy acid is fairly soluble in nitrobenzene, and soluble in sodium carbonate, whose warm solution precipitates the sodium salt in leaflets on cooling. Its aqueous solution gives no colour with ferric chloride solution.

6-CHLORO-4-HYDROXYQUINOLINE.

cf. Riegel et al., J.A.C.S., 1946, 68, 1264.
Duffin and Kendall, J.C.S., 1948, 893.

6-Chloro-4-hydroxyquinoline-3-carboxylic acid (12 gm.) was decarboxylated by heating in boiling diphenyl/diphenyl ether mixture. Decarboxylation proceeded somewhat slowly, and heating was maintained for 3 hours, after which period most of the solid had gone into solution. The dark liquid was cooled, diluted with light petroleum, and the insoluble product was filtered. This was extracted in the cold with dilute ammonia and filtered, leaving an insoluble portion which after washing and drying melted at 260-5°, without frothing or decomposition. The ammonium hydroxide filtrate, when acidified with dilute acetic acid, yielded a small white precipitate of m.p. 276°, with frothing. On admixture with a sample of 6-chloro-4-hydroxyquinoline-3-carboxylic acid (m.p. 276°), there was no depression of melting point, indicating that a small portion of the acid had remained undecarboxylated.

The crude 260-5° material on crystallisation from ethanol yielded pure 6-chloro-4-hydroxyquinoline in beautiful, long white glistening needles, which melted at 270-1°; 271° (Duffin and Kendall); 274-5° (Riegel et al.); 261-3° (Tarbell). Yield 7.2 gm. (75% of theory.)

The compound is insoluble in water, but is quite considerably soluble in hot, aqueous, sodium carbonate and ammonium hydroxide solution.

6-Chloro-4-hydroxyquinoline was later prepared by a 'continuous' method in which only the final end-product was isolated and identified. In this case, p-chloroaniline (6.37 gm.) and diethylethoxymethylene malonate (10.8 gm.) were dissolved in a mixture of diphenyl (60 gm.) and diphenyl ether (100 gm.), brought slowly to boiling point, and boiled under reflux for thirty minutes. After cooling to 100°, 10% aqueous sodium hydroxide (100 c.c.) was added carefully, and the heterogeneous mixture boiled vigorously for a further thirty minutes. (Complete solution was obtained after ten minutes.) The mixture was allowed to stand at room temperature overnight (convenience), after which period a slight flocculent precipitate had separated. This soon disappeared on warming on a water bath, however, and after treatment with decolourising charcoal, a dark liquid separated into two light-coloured, easily distinguishable layers. The cool reaction mixture was transferred to a separating funnel, and the layers were separated. The aqueous layer was acidified with acetic acid to yield 6-chloro-4-hydroxyquinoline-3-carboxylic acid, which was

collected on a nutsche, washed with water and placed in the oven to dry. The diphenyl/diphenyl ether layer was extracted with ether, washed several times with water until the washings were neutral to litmus, and the ethereal solution was dried over sodium sulphate. When dry, the 6-chloro-4-hydroxyquinoline-3-carboxylic acid was recombined with the dried diphenyl/diphenyl ether layer, together with an additional 40 c.c. of fresh solvent, and the mixture was boiled under reflux. All the solid material went into solution as decarboxylation occurred, a process which took three hours. On cooling to room temperature, the mixture was diluted with light petroleum (80-100°), and the insoluble 6-chloro-4-hydroxyquinoline was collected on a nutsche. It was resuspended in light petroleum, triturated, again collected and dried in the oven. After one crystallisation from ethanol, the compound melted at 268-70°, and weighed 6.3 gm., corresponding to an overall yield of 72%.

4:6-DICHLOROQUINOLINE.

cf. Riegel *et al.*, J.A.C.S., 1946, 68, 1264.
Tarbell, *ibid.*, 1946, 68, 1277.

6-Chloro-4-hydroxyquinoline (8.9 gm.) was refluxed gently in phosphorus oxychloride (20 c.c.), containing phosphorus pentachloride (10.4 gm.). After three hours, the solution was cooled, poured on to crushed ice to hydrolyse the phosphorus oxychloride, and stirred vigorously. The aqueous solution was treated with charcoal and filtered. On basification with ammonium hydroxide in the cold, 4:6-dichloroquinoline separated as a white, granular precipitate. After washing with ice water and drying in a vacuum desiccator over potassium hydroxide, the compound melted at 98-100°, and gave a crude yield of 8.7 gm. (87% theory). A small amount was crystallised from boiling cyclohexane to give colourless needles of m.p. 102-4°; 105° (Riegel *et al.*); 104-5° (Tarbell).

6-CHLORO-4-o-AMINOPHENYLAMINOQUINOLINE.

cf. Kermack and Smith, J.C.S., 1930, 1999.

4:6-Dichloroquinoline(9.9 gm.) was heated with o-phenylenediamine (5.4 gm.) at 140° under reduced pressure (20 mm.) for one hour. No reaction appeared to take place, but it was noticed that a considerable quantity of solid sublimed in the neck of the flask, and that more had collected in the side arm connecting the flask with the pump. A small portion of this sublimate was extracted with a spatula, and was found to melt at 100-104°; it was identical with 4:6-dichloroquinoline. The sublimate was returned to the body of the flask as completely as possible, and the melt was heated for a further one hour under reduced pressure. On cooling, water was added and the insoluble residue was dissolved in dilute hydrochloric acid, treated with charcoal, and filtered. The filtrate on basification with ammonia gave a white, granular precipitate of m.p. 98-102°, which did not depress the melting point of a pure sample of 4:6-dichloroquinoline. The product was thus assumed to be unchanged chloro compound. The aqueous filtrate on evaporation to dryness yielded solid material melting at 96-100°. which was assumed to be mainly unchanged o-phenylene diamine (m.p. 102°), since it is soluble in water.

The experiment just outlined was repeated with a trace of copper to act as catalyst:-

4:6-Dichloroquinoline (2.2 gm.) and o-phenylene diamine (1.2 gm.) were intimately mixed with a trace of copper bronze and placed in a flask, which was then evacuated at the pump and immersed in a oil bath at 140°. Almost immediately a vigorous reaction took place, the liquid frothed up, and, after spattering over the surface of the flask, set to a brittle mass. Heating was stopped, and solid was extracted with dilute hydrochloric acid, in which it was very soluble. On filtering and neutralising with ammonia, a solid separated which softened at 110° and melted at 178-80°. The compound was further purified by dissolving in dilute acetic acid, precipitating with ammonia, and finally crystallising from light petroleum, from which it separated in irregular plates of m.p. 186-7°. Yield 1.85 gm. (62% theory)

Found: C, 66.8; H, 4.35; N, 15.3.

$C_{15}H_{12}N_3Cl$ requires C, 66.8; H, 4.45; N, 15.58.

6-Chloro-4-aminophenylaminoquinoline is extremely soluble in ethanol, in which it exhibits a green fluorescence. It is insoluble in water, sparingly soluble in light petroleum, and soluble in benzene.

On one occasion when this experiment was carried out in the presence of copper, the product

precipitated from the hydrochloric acid solution by ammonia was found to melt at ca. 300°, and to be only partially soluble in ethanol. On extracting with this solvent a completely insoluble residue was left, melting at 320-40°.

The insoluble portion was also insoluble in water, benzene, acetone and ether, but soluble in acetic acid, from which it could be precipitated by alkali; and soluble in nitrobenzene from which it was crystallised. (m.p. 342-4°)

The solubilities of the compound suggested the presence of a large molecule with basic properties, and since it contained halogen (Beilstein's test), the only possible by-product appeared to be N:N'-bis-(6-chloroquinolyl)-o-phenylene diamine. This was later confirmed by analysis, and by the synthesis outlined in the next experiment.

Found: C, 67.2; H, 3.5; N, 12.75.

$C_{24}H_{16}N_4Cl_2$ requires C, 66.8; H, 3.7; N, 13.0.

N:N'-bis-(6-CHLOROQUINOLYL)-o-PHENYLENE DIAMINE.

6-Chloro-4-o-aminophenylaminoquinoline (0.54 gm) and 4:6-dichloroquinoline (0.4 gm.) were heated together under reduced pressure at 140° for 30 mins., in the presence of a trace of copper. The residual gum set solid on cooling and was extracted with dilute hydrochloric acid, treated with charcoal and basified with ammonium hydroxide. The white precipitate thus formed, was collected, washed with ethanol and dried. It melted at 300-320°. On crystallisation from nitrobenzene the compound yielded white needles of m.p. 342-4°, which on admixture with a sample of the by-product (m.p. 342-4°) isolated in the previous experiment showed no depression of melting point. (342-4°) Yield 0.64 gm. (80% of theory.)

Found: C, 67.1; H, 3.5; N, 12.7.

$C_{24}H_{16}N_4Cl_2$ requires C, 66.8; H, 3.7; N, 13.0.

N:N'-bis-(6-Chloroquinolyl)-o-phenylene diamine is insoluble in ethanol, methanol, water, acetone, benzene, chloroform and ether, but soluble in hot pyridine and hot nitrobenzene. It is soluble in dilute acids, from whose solutions it may be precipitated with alkali.

N:N'-bis-(6-CHLOROQUINOLYL)-o-PHENYLENE DIAMINE.

METHIODIDE.

N:N'-bis-(6-Chloroquinolyl)-o-phenylene diamine (0.55 gm.) was dissolved in nitrobenzene (150 c.c.) at 180°. The solution was cooled to 100° without any precipitation taking place, and dimethyl sulphate (1 gm.≡3 gm. mol.) was added. The mixture was heated under reflux at 130° for 2 hours, and then allowed to cool to room temperature. On standing for 12 hours, a dark red oil separated, which was extracted with water and the combined aqueous extracts concentrated to small volume. When potassium iodide in a saturated aqueous solution was added, a yellow precipitate formed, which was separated, washed and dried. The product melted at 310° with frothing. After three crystallisations from water, the methiodide melted at 330-2°, and was found to be the dihydrate of the dimethiodide of N:N'-bis-(6-chloroquinolyl)-o-phenylene diamine. Yield 0.71 gm. (78% theory.)

Found: C, 41.4; H, 3.2.

$C_{24}H_{16}N_4Cl_2.2CH_3I.2H_2O$ requires C, 41.6; H, 3.4.

On further recrystallisation, a red flocculent precipitate separated, which was hand picked from the yellow crystals. The product melted at 190°. On redissolving and seeding with the methiodide, a homogeneous mass of yellow crystals again resulted

on cooling. As this red product was obtained only in traces, it has not been possible to investigate it further.

The dimethiodide is soluble in ethanol and in water, from which solution an orange precipitate is formed on basification with strong sodium hydroxide.

M.p. 285°

6-CHLORO-4-(BENZTRIAZOLYL-1')QUINOLINE.

cf. Kermack and Smith, J.C.S., 1930, 1999.

Crude 6-chloro-4-o-aminophenylaminoquinoline (6.7 gm.) was dissolved in 3% hydrochloric acid (100 c.c.), treated with charcoal to remove a brown colouration, filtered and cooled to 5°. A solution of sodium nitrite (2.6 gm.) in water (10 c.c.) was added slowly with stirring until a slight excess was present. After standing at room temperature for 2 hours, the white , gelatinous precipitate of the base was filtered, and found to melt at 180-5°. On crystallisation from ethanol, 6-chloro-4-(benztriazolyl-1')quinoline separated in long white needles melting at 185-6°. Yield 4 gm. (56% of theory.)

Found: C, 64.1; H, 2.9; N, 19.7.

$C_{15}H_9N_4Cl$ requires C, 64.2; H, 3.3; N, 19.9.

This base is soluble in cold, dilute acetic, nitric, hydrochloric and sulphuric acids, in ethanol and benzene; it is sparingly soluble in light petroleum, and is insoluble in water and hot 2N sodium hydroxide.

15-CHLORO-2:3-BENZ-γ-CARBOLINE.

cf. Kermack and Smith, J.C.S., 1930, 1999.

6-Chloro-4-(benztriazolyl-1')quinoline (2 gm.) was heated in boiling, syrupy phosphoric acid (20 c.c.) until the effervescence ceased. The resulting dark liquid was poured into a large excess of water to give a white precipitate, which was collected on a nutsche, washed with water and dried. 15-Chloro-2:3-benz-γ-carboline, melting with sublimation above 360°, was purified by crystallisation from aqueous pyridine, from which it separated in small white needles. Yield 1.26 gm. (70% theory.)

Found: C, 71.4; H, 3.4; N, 10.9.

$C_{15}H_9N_2Cl$ requires C, 71.3; H, 3.6; N, 11.1.

The base is only very sparingly soluble in either dilute or concentrated hydrochloric, nitric or acetic acids. It is insoluble in alkali, benzene and ether, but it is moderately soluble in ethyl and methyl alcohol in which solutions it exhibits no fluorescence even under the arc light. It is soluble in hot pyridine and hot nitrobenzene.

15-CHLORO-4-METHYL-2:3-BENZ-γ-ISOCARBOLINE.

15-Chloro-2:3-benz-γ-carboline (0.5 gm.) was treated with methyl iodide (2 c.c.) while dissolved in the minimum amount of nitrobenzene. A crystalline precipitate gradually separated from the reaction mixture, which after 4 hour's heating at 100° was filtered. 15-Chloro-2:3-benz-γ-carboline methiodide thus obtained melted at 255° when pure. An aqueous solution of the salt was basified to yield a yellow material, which was filtered, washed, dried and crystallised several times from dry benzene. After being dried in a vacuum at 80° for 4 hours over P_2O_5, the product melted at 245°.

Found: C, 67.3; H, 4.3.

$C_{16}H_{11}N_2Cl.H_2O$ requires C, 67.5; H, 4.6.

15-Chloro-4-methyl-2:3-benz-γ-isocarboline is soluble in benzene and sparingly soluble in light petroleum. It is also soluble in ethanol.

15-CHLORO-4-DIETHYLAMINOETHYL-2:3-BENZ-γ-ISOCARBOLINE.

Diethylaminoethyl chloride (0.14 gm.) and 15-chloro-2:3-benz-γ-carboline (0.25 gm.) were heated in nitrobenzene (50 c.c.) under reflux for 9 hours at 100°. The solution was allowed to stand at room temperature overnight. The precipitate of the hydrochloride which had separated was filtered, washed with ether and dried. M.P. 262°, with frothing. The base was obtained by dissolving the hydrochloride in water and precipitating with amminium hydroxide, a procedure which frees the product from the by-product 1:4-tetraethylpiperazinium dichloride. This compound is formed by the condensation of two molecules of side chain and is completely soluble in ammonium hydroxide. The base, a yellow solid, softened at 40° and melted at 70-90°. On crystallisation from aqueous ethanol, softening again occurred at 40° followed by melting at 69-71°. On drying in a vacuum desiccator over potassium hydroxide, and subsequent crystallisation from light petroleum (60/80) the melting point rose to 125-6°. Yield 0.3 gm. (82% theory)

Found: C, 71.4; H, 5.9; N, 11.8.

$C_{21}H_{22}N_3Cl$ requires C, 71.7; H, 6.3; N, 11.95.

15-Chloro-4-diethylaminoethyl-2:3-benz-γ-isocarboline is soluble in ethanol, benzene and light petroleum and fluoresces in dilute acetic acid.

15-CHLORO-1-DIETHYLAMINOETHYL-2:3-BENZ-γ-CARBOLINE.

cf. Dewar, J.C.S., 1944, 619.

Diethylaminoethyl chloride (0.14 gm.) was added to a mixture of 15-chloro-2:3-benz-γ-carboline (0.25 gm.) and finely ground sodamide (0.03 gm.) in toluene (10 c.c.). The mixture was heated at 70° for 30 minutes, raised to 115° for a further 30 mins., and was refluxed at 110° for 4 hours. After cooling water was added, and the insoluble, unchanged material filtered off. The toluene layer, separated from the aqueous phase, was extracted with 5% acetic acid, from which the base was precipitated by ammonium hydroxide. For further purification the base was re-extracted with ether, dried over anhydrous potassium carbonate, and after removal of the solvent, was crystallised from aqueous ethanol. Yield 0.27 gm. (77% theory.) 15-Chloro-1-diethylaminoethyl-2:3-benz-γ-carboline is a white crystalline base, melting at 114-5°. It depresses the melting point of 15-chloro-4-diethylaminoethyl-2:3-benz-γ-isocarboline obtained in the previous experiment.

Found: C, 71.3; H, 5.95; N, 11.6.

$C_{21}H_{22}N_3Cl$ requires C, 71.7; H, 6.3; N, 11.95.

ETHYL 4-CHLOROQUINOLINE-3-CARBOXYLATE.

Ethyl 4-hydroxyquinoline-3-carboxylate (5.4 gm.) prepared as described on page 131, was added to a solution of phosphorus pentachloride (5.2 gm.) in phosphorus oxychloride (10 c.c.), and the mixture refluxed gently for two hours. When cold, the solution was poured on to crushed ice with vigorous stirring, and after decolourisation with charcoal was basified with dilute sodium hydroxide. The precipitate which settled was white in colour and melted at 35-8°. Yield 3 gm. (50% theory). The base was crystallised from light petroleum (40/60°), from which it separated in large, white prisms. M.P. 37°.

Found: C, 61.1; H, 3.9; N, 5.6.

$C_{12}H_{10}O_2NCl$ requires C, 61.15; H, 4.2; N, 5.9.

Ethyl 4-chloroquinoline-3-carboxylate is insoluble in aqueous sodium carbonate, sodium hydroxide and ammonium hydroxide. It is soluble in dilute hydrochloric acid (2N) in the cold, but on warming a white precipitate separates, which is insoluble in water but soluble in alkali.

ATTEMPTS TO PREPARE 4-CHLOROQUINOLINE-3-CARBOXYLIC ACID FROM ITS ESTER.

Two pilot experiments were carried out in an attempt to prepare this acid from its ester.

1. Ethyl 4-chloroquinoline-3-carboxylate (0.5gm.) was warmed on a water bath with aqueous sodium hydroxide (5%) until complete solution was obtained, and was then heated for a further 15 minutes, making a total of two hours. The solution was treated with charcoal, filtered hot, and acidified with dilute acetic acid. The small white precipitate which separated was filtered, washed with water and dried in a vacuum desiccator over potassium hydroxide. The product, which melted at 260° with effervescence, was found to be devoid of chlorine by Beilstein's test, and by a silver nitrate test carried out on the filtrate from a sodium fusion experiment. A small portion of it was crystallised from nitrobenzene, when a m.p. of 266-8° was recorded. A sample of this material when intimately mixed with an authentic specimen of 4-hydroxyquinoline-3-carboxylic acid showed no depression in melting point, decomposing with frothing at 266-70°.

2. A solution of ethyl 4-chloroquinoline-3-carboxylate (0.5 gm.) in dilute hydrochloric acid (2N) was refluxed for one hour, charcoaled and filtered hot through a fluted paper. On cooling, a white precipitate which had separated was filtered, washed

with water and dried in vacuo. M.P. 269°, with effervescence. A mixture of this solid and 4-hydroxyquinoline-3-carboxylic acid melted at 268-70°, showing no depression and indicating that the chlorine group had again been replaced by a hydroxyl .

Various other experiments on similar lines, employing different temperatures and concentrations of acid and alkali, were carried out, but in no case was it possible to isolate the hitherto unknown 4-chloroquinoline-3-carboxylic acid. Whenever hydrolysis of the esther group occurred, the chlorine was replaced by a hydroxyl radical.

ETHYL 4-ANILINOQUINOLINE-3-CARBOXYLATE.

Finely ground ethyl 4-chloroquinoline-3-carboxylate (2.3 gm.) was added as quickly as possible to freshly distilled aniline (0.93 gm.) and stirred rapidly to obtain complete mixing. A few seconds after the addition a vigorous reaction took place, considerable heat was evolved, and the mixture frothed up to set almost immediately to a hard, golden gum, which on scratching and triturating with ether yielded the hydrochloride of ethyl 4-anilinoquinoline-3-carboxylate as a yellow powder. M.P. 145-8°. The free base, obtained as a yellow gelatinous precipitate by the addition of ammonium hydroxide to a hot aqueous solution of the hydrochloride, separated from ethanol in the form of short yellow prisms, m.p. 99-100°. Yield 2.25 gm. (77% of theory.)

Found: C, 74.0; H, 5.5; N, 9.6.

$C_{18}H_{16}O_2N_2$ requires C, 73.7; H, 5.5; N, 9.9.

Ethyl 4-anilinoquinoline-3-carboxylate is soluble in dilute acids, from which it may be precipitated by alkali. It is insoluble in ether and water, but readily soluble in ethanol.

4-ANILINOQUINOLINE-3-CARBOXYLIC ACID.

Ethyl 4-anilinoquinoline-3-carboxylate (2 gm.) was refluxed for one hour with 5% ethanolic sodium hydroxide. The ester gradually went into solution, leaving a clear, yellow-brown liquid. On treating with charcoal and filtering hot through a fluted filter paper, the solution was neutralised with dilute acetic acid to yield a soapy, gelatinous precipitate, m.p. 257-62°. Yield 1.6 gm. (90% of theory.)

Attempts to crystallise the product were unsuccessful, the hot solution either cooling to form a solid gel, or precipitating as a flocculent precipitate. The product was therefore purified by taking up in dilute hydrochloric acid and precipitating with a saturated solution of sodium acetate. As the melting point was still somewhat indefinite, 260-5°, with frothing, a small portion of the acid was decarboxylated by heating in a test tube at its melting point till the effervescence of carbon dioxide ceased. The melting point of the resulting 4-anilinoquinoline was 196-8°, which agrees with that recorded in the literature, i.e. 198°. (Ephraim, Ber., 26, 2229.(1893).)

2:3:4':3'-QUINOQUINOLO-4-ONE.

4-anilinoquinoline-3-carboxylic acid (0.5 gm.) was heated at 95° with concentrated sulphuric acid for 30 minutes. It was noticed that a blue fluorescence developed in the solution, which intensified as the heating continued. On cooling, the solution was poured into crushed ice and stirred well. The clear aqueous solution was rendered alkaline with ammonium hydroxide and the resulting white, gelatinous precipitate collected on a filter paper at the pump. In order to isolate the product, the filter paper was digested with ethanol in the hot, and after filtering, the solution was allowed to stand for 12 hours. Needles separated, which were filtered, washed with ethanol and dried. M.P. above 360°. On recrystallising from ethanol, long, slender white fibres separated, which on drying either in the air or *in vacuo* turned a bright yellow. When moistened with water, the yellow colour disappeared and the colourless compound was regenerated. M.P. above 360°, with marked decomposition. Yield 0.25 gm. (65% of theory.)

Found: C, 73.7; H, 4.2; N, 10.0.

$C_{16}H_{11}N_2O.\frac{3}{4}H_2O$ requires C, 74.0; H, 4.05; N, 10.6.

2:3:4':3'-quinoquinolo-4-one is insoluble in aqueous sodium carbonate or hydroxide, very sparingly soluble in hydrochloric acid (2N), soluble in concentrated sulphuric acid, in which it exhibits a light

blue fluorescence, and soluble in ethanol. In this solvent it shows a very marked sky blue fluorescence, immediately destroyed when a drop of dilute hydrochloric acid is added to the solution. A trace of sodium hydroxide solution does not have the same effect.

On repeating the experiment, 100% sulphuric acid was used in error as cyclising agent instead of concentrated sulphuric acid. When poured into ice water a large white precipitate formed, which did not dissolve even on warming. It was filtered, washed with water and dried. M.P. above 400°.

The product is soluble in hot aqueous sodium carbonate and cold sodium hydroxide solution (2N), from which it may be precipitated by acetic acid. The compound is insoluble in hydrochloric acid (concentrated or dilute), or in hot water. A sample was fused with sodium and the aqueous filtrate was found to give a positive sulphur reaction. The compound was assumed to be a sulphonated derivative.

4-CHLORO-2:3:4':3'-QUINOQUINOLINE.

4-Anilinoquinoline-3-carboxylic acid (1 gm.) was refluxed gently with phosphorus oxychloride (5 c.c.) for 2 hours, during which time a yellow solid separated on the sides of the flask. The excess phosphorus oxychloride was distilled off under reduced pressure at 80°, and the residual yellow powder sucked as dry as possible at the pump. The residue was triturated with cold 20% sodium hydroxide, care being taken that it was made definitely alkaline before it had any chance to heat up on coming in contact with the water. In this way, hydrolysis to the quinoquinolone was reduced to a minimum. The brownish-red solid was filtered on a sintered funnel, thoroughly washed with water until the filtrate was neutral, and dried over potassium hydroxide in a vacuum desiccator. The compound gave a positive halogen test (Beilstein), and melted between 300 and 327°.

The powder was digested with hot benzene in the presence of a pellet of potassium hydroxide, and filtered hot. On concentrating the filtrate to a small volume and allowing to cool, needles of 4-chloro-2:3:4':3'-quinoquinoline separated, m.p. 210-5°. The base was recrystallised from dry toluene, from which solvent it formed beautiful, pale yellow cubes, m.p. 210°. Yield 0.67 gm.

Yield 0.67 gm. (67% of theory.)

Found: C, 73.2; H, 3.2; N, 10.2.

$C_{16}H_9ON_2$ requires C?72.6; H, 3.4; N, 10.6.

The residue from the hot benzene filtrate melted at above 360°, and fluoresced with concentrated sulphuric acid. It proved to be 2:3:4':3'-quinoquinolone.

4-Chloro-2:3:4':3'-quinoquinoline is soluble in cold, dilute acid, ethanol, hot benzene and toluene, in which solutions it exhibits a green fluorescence; it is insoluble in dilute alkali and light petroleum.

4-Chloro-2:3:4':3'-quinoquinoline was also synthesised by refluxing 2:3:4':3'-quinoquinolone (prepared as described on page 187) with phosphorus oxychloride and pentachloride for 6 hours in an oil bath, and working up as described above.

The stability of the halogen atom in 4-chloro-2:3:4':3'-quinoquinoline is shown in the experiments described below.

The compound (0.5 gm.) was heated with 2N sodium hydroxide (5 c.c.) at 100°. After 2 hours the undissolved material was filtered off, washed with water and dried. The yellow residue melted at 210°, and when mixed with an authentic specimen of 4-chloroquinoquinoline, m.p.210°, showed no depression in melting point. This indicates the stability

of this type of compound to alkaline solutions.

In another experiment, the compound (0.5 gm.) was refluxed at 100° with ethanol. The solid dissolved immediately to give a clear, pale yellow solution which was heated for 2 hours. On cooling, the crystals which separated were filtered, washed and dried. The compound was found to be insoluble in dilute sodium hydroxide, to give a positive Beilstein test and to melt at 210°, not depressed on admixture with an analytically pure sample of 4-chloro-2:3:4':3'-quinoquinoline. This shows that the compound is relatively stable when refluxed with alcohol (in presence of a trace of water).

That 4-chloro-2:3:4':3'-quinoquinoline is unstable towards acid media is shown by the following experiment. When heated with 2N hydrochloric acid at 100°, a solid started to separate from the originally clear solution after 5 minutes. The heating was continued for 2 hours, after which time the mixture was cooled and filtered. The residue, which was washed with water and dried, melted at 375-90° and gave a positive Beilstein test. On grinding with dilute sodium hydroxide in a mortar, however, a compound melting above 360° was obtained, which contained no chlorine and was identical with 2:3:4':3'-quinoquinolone. The warm hydrochloric acid had evidently hydrolysed the chloro compound giving the hydrochloride of 2:3:4':3'-quinoquinolone.

ETHYL 4-CHLORO-6-METHOXYQUINOLINE-3-CARBOXYLATE.

Ethyl 4-hydroxy-6-methoxyquinoline-3-carboxylate (15.5 gm.) prepared as described on page 153, was added to phosphorus pentachloride (13 gm.) in phosphorus oxychloride (20 c.c.) and heated at 150° for 6 hours. When cold, the homogeneous solution was poured on to crushed ice and the oxychloride allowed to decompose. Some tar which separated was filtered, and the filtrate was basified with ammonium hydroxide. The white precipitate which formed melted at 85-6°, after crystallising from light petroleum (80/100°), and drying in vacuo. Yield 13.42 gm. (80% of theory.)

Found: N, 5.4.

$C_{13}H_{12}O_3NCl$ requires N, 5.3.

The chlorine in this compound was found to be unstable as shown by the fact that if placed in the oven at 60° while still contaminated with water, conversion to the hydroxy compound took place readily.

The ester is soluble in benzene and the higher boiling petroleum fractions. It is soluble in aqueous sodium hydroxide (2N-) and dilute sodium carbonate on warming. It is also soluble in dilute acetic acid on warming, depositing long, colourless needles on cooling.

ATTEMPTED PREPARATIONS OF 6-METHOXY-4-CHLOROQUINOLINE-3-CARBOXYLIC ACID.

In an attempt to prepare this chloro acid, ethyl 6-methoxy-4-chloroquinoline-3-carboxylate (0.2 gm.) was dissolved in 2N hydrochloric acid (2 c.c.) in the cold, and allowed to stand at room temperature for 3 weeks. Large white crystals which separated were filtered off, washed with water and dried on a porous plate. M.P. 280°. The product was found to be soluble in cold sodium carbonate, from which it was reprecipitated with acetic acid. (M.P. 278-80°) No chlorine was detectable. A small amount on admixture with a sample of 6-methoxy-4-hydroxyquinoline-3-carboxylic acid (M.P. 276-8°) showed no depression, indicating that the hydroxy compound had been formed instead of the desired 6-methoxy-4-chloroquinoline-3-carboxylic acid.

2. 6-Methoxy-4-hydroxyquinoline-3-carboxylic acid (0.5 gm.) was heated for 7 hours in excess phosphorus oxychloride (10 c.c.). The solution developed a green fluorescence, and deposited a yellow compound on the sides of the flask, which on cooling became contaminated with a brown oil. The contents of the flask were poured into chilled, dilute sodium carbonate solution (1N). A pale yellow solid separated, which after standing at room

temperature for 2 hours was collected, washed with ice water and dried in vacuo over calcium chloride. M.P. 276°.

The product gave a positive halogen test (Beilstein) but was insoluble in water, sodium carbonate and sodium hydroxide (10N), even on boiling. The compound was readily soluble in dilute hydrochloric acid and in sulphuric acid; this orange solution showed a faint green fluorescence on dilution. The nature of this compound was not further investigated, but it was thought to be a higher chlorinated product.

The original sodium carbonate filtrate on acidification with dilute acetic acid yielded a white crystalline precipitate, m.p. 270-2°, and proved to be 6-methoxy-4-hydroxyquinoline-3-carboxylic acid.

ETHYL 6-METHOXY-4-ANILINOQUINOLINE-3-CARBOXYLATE.

When finely powdered ethyl 6-methoxy-4-chloroquinoline-3-carboxylate (4.3 gm.) and aniline (1.6 gm.) were intimately mixed, the mixture heated up spontaneously and set to a hard gum. On triturating with ether, a yellow hydrochloride separated melting at 185-8°. The base, obtained as a white powder by the addition of ammonium hydroxide to the hot aqueous solution of the hydrochloride, separated from ethanol in the form of colourless prisms, m.p. 101°. Yield 3.6 gm. (69% theory.)

Found: N, 8.5.

$C_{19}H_{18}O_3N_2$ requires N, 8.7.

Ethyl 6-methoxy-4-anilinoquinoline-3-carboxylate is soluble in dilute mineral acids, from which solutions it may be precipitated by alkali.

6-METHOXY-4-ANILINOQUINOLINE-3-CARBOXYLIC ACID.

Ethyl 6-methoxy-4-anilino-3-carboxylate (20 gm.) was hydrolysed to the acid by refluxing with 5% ethanolic sodium hydroxide (100 c.c.) for two hours. On cooling, the clear, light brown solution was acidified with acetic acid to give 6-methoxy-4-anilinoquinoline-3-carboxylic acid, which after washing and drying melted at 200°. Yield 17.5 gm. (96% of theory.)

Attempts to crystallise the compound were unsuccessful. Purification was accomplished by repeatedly dissolving the gel in dilute sodium carbonate and reprecipitating the acid with dilute acetic acid. 6-Methoxy-4-anilinoquinoline-3-carboxylic acid after thorough drying in vacuo at 60° over P_2O_5 melted at 264° with frothing.

Found: C, 65.1; H, 4.9; N, 9.2.

$C_{17}H_{14}O_3N_2.H_2O$ requires C, 65.3; H, 5.1; N, 9.0.

The acid is soluble in hot ethanol, sparingly soluble in benzene and is soluble in pyridine.

A small portion of the acid was decarboxylated by heating in a test tube at its melting point until the effervescence ceased. The resulting 6-methoxy-4-anilinoquinoline, after crystallisation from ethanol, melted at 220°. The hydrochloride of this base melted at ca. 215°.

6'-METHOXY-2:3:4':3'-QUINOQUINOLO-4-ONE.

6-Methoxy-4-anilinoquinoline-3-carboxylic acid (0.5 gm.) was heated on the water bath with concentrated sulphuric acid (5 c.c.) for 30 minutes. On cooling, the solution was poured on to crushed ice and basified with ammonium hydroxide. A white granular precipitate separated, which was filtered, washed with water and dried. The product darkened and charred appreciably when heated to 310°, but appeared to melt with decomposition at 340-60°. After several crystallisations from ethanol, 6'-methoxy-2:3:4':3'-quinoquinolo-4-one was found to melt at 350° with marked decomposition.

Yield 0.29 gm. (62% of theory.)

Found: C, 74.0; H, 4.5; N, 9.7.

$C_{17}H_{12}O_2N_2$ requires C, 73.9; H, 4.4;

4-CHLORO-6'-METHOXY-2:3:4':3'-QUINOQUINOLINE.

6-Methoxy-4-anilinoquinoline-3-carboxylic acid (1 gm.) was cyclised by heating in phosphorus oxychloride (30 c.c.) for four hours. After the reaction was complete, the excess phosphorus oxychloride was removed by distillation under reduced pressure at 100°, and the residue - an orange solid - was triturated with cold 20% aqueous sodium hydroxide, care being taken to avoid local heating. The yellow solid which resulted was collected on a sintered glass funnel, well washed with water and dried *in vacuo* over potassium hydroxide. M.P. 175°.
The chloro compound was separated from a trace of 6'-methoxy-2:3:4':3'-quinoquinolone by extracting with dry benzene over a pellet of potassium hydroxide. On crystallising from toluene, 4-chloro-6'-methoxy-2:3:4':3'-quinoquinoline separated in long, shining yellow needles of m.p. 177-8°. Yield 0.5 gm. (50% theory.)

Found: C, 66.9; H, 3.7; N, 8.6.
67.1; H, 4.3; N, 8.5.

$C_{17}H_{10}ON_2Cl.\frac{1}{2}H_2O$ requires C, 67.2; H, 3.95; N, 9.2.

The chloro compound shows a marked green fluorescence in ethanol and ether. It will withstand prolonged boiling in dilute alkali, but it is converted into 6'-methoxy-2:3:4':3'-quinoquinolone on heating with dilute acids.

THE CONVERSION OF 6'-METHOXY-2:3:4':3'-QUINOQUINOLONE INTO 4-CHLORO-6'-METHOXY-2:3:4':3'-QUINOQUINOLINE.

Two experiments were conducted here to ascertain whether 'Cetavlon' (cetyltrimethylammonium bromide) had a beneficial effect on the reaction.

1. Crude 6'-methoxy-2:3:4':3'-quinoquinolone (2.75gm.) was heated at 160° with phosphorus pentachloride (2 gm.) and phosphorus oxychloride (30 c,c.) for nine hours. The solid did not all go into solution. After removing the excess oxychloride under reduced pressure, the residual yellow solid was added in small portions to a mixture of equal volumes of ammonium hydroxide (conc.) and chloroform. A considerable amount of material remained out of solution, and was filtered off at the pump. The filtrate was transferred to a separating funnel, and the layers separated. The chloroform layer, after washing twice with water, was dried over sodium sulphate and evaporated to dryness. The yield of the resulting brownish-yellow crystals, melting at 170-5°, was 0.9 gm., which corresponds to 31% yield. On crystallisation from toluene, the needles melted at 177-8°, and showed no depression in melting point with a pure sample of 6'-methoxy-4-chloro-2:3:4':3'-quinoquinoline. The insoluble residue was found to be unchanged 6'-methoxy-2:3:4':3'-quinoquinolone, and weighed

1 gm. (34% yield.)

2. Crude 6'-methoxy-2:3:4':3'-quinoquinolone (2.75 gm.) was added to a mixture of phosphorus pentachloride (2 gm.), phosphorus oxychloride (30 c.c.) and 'Cetavlon' (0.1 gm.). The mixture was heated at 160° for nine hours, after which period the excess phosphorus oxychloride was distilled off under reduced pressure, and the residue was added by degrees to an ammonium hydroxide/ice/chloroform mixture. At this stage some undissolved material was filtered off, which melted above 300° and which was unchanged starting material (0.6 gm.). The chloroform layer was separated from the aqueous phase, washed with water, and dried over sodium sulphate. On evaporating to dryness, a yellow crystalline solid remained, melting at 175-8°, and weighing 1.4 gm. (47% yield.). This, on crystallisation from toluene, melted at 176-8°, and did not depress the melting point of a pure sample of 6'-methoxy-4-chloro-2:3:4':3'-quinoquinoline.

The crude material from the second experiment appeared to be purer than that from the first, being somewhat cleaner-looking in colour, and melting slightly higher. The yield was also appreciably better, 47% compared with 31%, an increase of approximately 50%.

ATTEMPTED PREPARATION OF ETHYL 4:6-DICHLOROQUINOLINE-3-CARBOXYLATE.

Ethyl 6-chloro-4-hydroxyquinoline-3-carboxylate (8.4 gm.) was prepared as described on page 165, and was heated with phosphorus pentachloride (7 gm.) and phosphorus oxychloride (20 c.c.) at 150° for seven hours. The cooled homogeneous liquid was poured into water and ice, and the clear solution treated with charcoal and filtered. During neutralisation with ammonium hydroxide, the solution warmed up rather more than was anticipated, the maximum temperature of 80° being reached. This was reduced to 10°, however, by the addition of ice, and the experiment was continued. When the solution was alkaline to litmus, the copious white precipitate which separated was filtered, washed with water and dried in a vacuum desiccator. The product melted with effervescence at 260-70°, dissolved readily in warm aqueous sodium carbonate, but not in dilute hydrochloric acid. On crystallisation from ethanol, the compound was found to soften at 260° and melt with effervescence at 278-9°. The product was identical in all respects with 6-chloro-4-hydroxyquinoline-3-carboxylic acid (m.p. 279°). This indicated that both the chloro and the ester groupings had been hydrolysed in the working up of the experiment to give 6-chloro-4-hydroxyquinoline-3-carboxylic acid in 90% yield.(6.8 gm.)

4:6-DICHLOROQUINOLINE-3-CARBOXYLIC ACID.

6-Chloro-4-hydroxyquinoline-3-carboxylic acid (5 gm.), isolated in the previous experiment, was treated with phosphorus pentachloride (5.2 gm.) and phosphorus oxychloride (15 c.c.) by gently refluxing together for 5 hours. When cold, the solution was poured into ice and water and stirred well; the resulting white precipitate which did not go into solution on standing was filtered, washed and dried in a vacuum desiccator over potassium hydroxide. The product melted at 280-2° and dissolved readily in warm sodium carbonate solution, from which no precipitate separated on cooling (cf. 6-chloro-4-hydroxyquinoline-3-carboxylic acid). It was insoluble in dilute hydrochloric acid, but dissolved readily in ethanol. unlike the 6-chloro-4-hydroxy- acid. A mixture of the two acids melted at 274°, giving a depression of 4°. When an attempt was made to purify a small portion of the product by crystallisation from hot ethanol, however, it was found that although the compound dissolved completely in the first instance, a white, voluminous precipitate which separated almost immediately afterwards would not dissolve in the same volume of ethanol. On filtering, this product was found to be 6-chloro-4-hydroxyquinoline-3-carboxylic acid, m.p. 278-9°.

It was concluded from the above evidence, that the product originally obtained was indeed 4:6-dichloroquinoline-3-carboxylic acid, which, on account of the instability of the chlorine atom, may be easily hydrolysed to 6-chloro-4-hydroxyquinoline-3-carboxylic acid, e.g. by heating in ethanol in the presence of a trace of water. In view of this, it was decided to carry on to the next stage in the experiment without further purification.

Yield of 4:6-dichloroquinoline-3-carboxylic acid: 5 gm. (80% of theory.)

6'-CHLORO-2:3:4':3'-QUINOQUINOLO-4-ONE.

6-Chloro-4-anilinoquinoline-3-carboxylic acid (0.5 gm.) was heated at 95° with concentrated sulphuric acid (5 c.c.) for 30 minutes. A blue fluorescence developed in the solution.

On cooling, the solution was poured into crushed ice and stirred well. The clear, aqueous solution was basified with ammonium hydroxide, and the resulting white precipitate was collected, washed with water and dried. M.P. above 360°. On crystallisation from ethanol, 6'-chloro-2:3:4':3'-quinoquinolone separated as stout white needles, melting above 360°.

Found: N, 10.0.

$C_{16}H_9ON_2Cl$ requires N, 10.0.

6'-Chloro-2:3:4':3'-quinoquinolone is insoluble in aqueous sodium carbonate or sodium hydroxide solutions, very sparingly soluble in acetic acid, but soluble in concentrated sulphuric acid, exhibiting a blue fluorescence. The compound is sparingly soluble in ethanol, in which it shows a blue fluorescence.

THE PREPARATION OF 4:6'-DICHLORO-2:3:4':3'-QUINOQUINOLINE FROM 6'-CHLORO-2:3:4':3'-QUINOQUINOLONE.

Crude 6'-chloro-2:3:4':3'-quinoquinolone (3 gm.) was heated for 7 hours with a trace of 'Cetavlon' (0.1 gm.) in phosphorus oxychloride. The excess of the latter was then distilled off under reduced pressure to leave a brown solid. This residue was scraped into equal volumes of chilled ammonium hydroxide and chloroform, and the insoluble material extracted with more chloroform. The combined extracts were then filtered to free them from undissolved matter, separated and dried over anhydrous sodium sulphate. On evaporation, a small amount of 4:6'-dichloro-2:3:4':3'-quinoquinoline remained, of melting point 236-8°. Yield 1.0 gm. The chloroform insoluble residue, after washing with water and drying in the oven, melted above 360° and weighed 0.9 gm. It was unchanged starting material.

THE ATTEMPTED PREPARATION OF 4-DIETHYLAMINOETHYL-AMINO-2:3:4':3'-QUINOQUINOLINE.

cf. Dobson and Kermack, J.C.S., 1946, 150.

Freshly distilled phenol (5 gm.) was heated *in vacuo* on a boiling water bath, and after 2 hours, diethylaminoethylamine (0.46 gm., twofold excess.) was added, and the contents of the flask kept at 100° under vacuum for a further two hours. *4-Chloro-2:3:4';3'-quinoquinoline* (0.5 gm.), previously dried in a vacuum desiccator over potassium hydroxide for 48 hours, was introduced, and the mixture heated at 100° under reflux. After 15-20 minutes, the chloro compound had all dissolved, and the reddish solution was occasionally shaken. A marked reaction for chloride ions was given by a test portion after 4 hours, when the heating was stopped. The cooled solution was poured into 2N sodium hydroxide (30 c.c.), whereupon an oily suspension formed which was extracted immediately with ether. The base was further purified by shaking the ethereal extract with 5% acetic acid, precipitating with ammonium hydroxide and reextracting with ether. The ethereal solution was dried over anhydrous potassium carbonate, and the ether removed by distillation. The yellow oil which remained did not crystallise on scratching or standing, and it was therefore dissolved in dilute acetic

in an attempt to form the acetate, and evaporated to dryness under reduced pressure at 60°. A solid residue which remained was triturated with ethanol and filtered. The product, in the form of white, shining needles, melted above 360°, dissolved in concentrated sulphuric acid to give a blue fluorescent solution, and was insoluble in dilute acetic acid. It was evidently 2:3:4':3'-quinoquinolo-4-one, the side chain having been removed by the prolonged contact with hot acetic acid.

The above experiment was repeated, and after removing the ether by distillation, the residual yellow oil was placed under vacuum at 100° to remove any excess ethylamine base. The oil was repeatedly dissolved in hot light petroleum (80/100°) and allowed to cool, whereby crystallisation was ultimately induced and the oil gradually solidified. On subsequent crystallisation from light petroleum, the crystals appeared to soften at 60-4°, and melt at 81°. The material was passed through an alumina column with benzene, but no separation into bands occurred, the single yellow band passing cleanly through. The benzene was distilled off to leave yellow, rod-shaped crystals which again softened at 60-2° and appeared to melt finally at 80-1°. The melting point of the compound after drying for 12 hours at 60° over P_2O_5 *in vacuo* was taken on a

Köfler type micro apparatus, and it was then seen to soften at 45°, melt at 60-5°, solidify at 70-5° and melt finally at 80-1°.

The product is soluble in most organic solvents, and exhibits a marked blue fluorescence in ethanol and ether. It is soluble in dilute acids, showing a strong green fluorescence in dilute acetic acid solution.

Found: C, 76.65; H, 6.6; N, 14.9.

$C_{22}H_{24}N_4$ requires C, 76.7; H, 6.9; N, 16.3.

$C_{22}H_{24}N_4.C_{22}H_{23}ON_3$ requires C, 76.5; H, 6.6; N, 14.9.

$C_{22}H_{24}N_4.C_{16}H_{10}ON_2$ " C, 77.3; H, 5.8; N, 14.2.

$C_{22}H_{24}N_4.C_{22}H_{14}ON_2.\frac{1}{2}H_2O$ " C, 77.2; H, 5.85; N, 12.2.

The significance of these results has already been discussed on page 117.

THE ATTEMPTED PREPARATION OF 6'-METHOXY-4-DIETHYL-AMINOETHYLAMINO-2:3:4':3'-QUINOQUINOLINE.

6'-Methoxy-4-chloro-2:3:4':3'-quinoquinoline (0.5 gm.), previously dried over potassium hydroxide, was added to a mixture of dry phenol (5 gm.) and diethylaminoethylamine (0.5 gm.), which had been dried in a vacuum at 100° for 2 hours. The reaction mixture was heated at 100° for 4 hours, cooled and poured into dilute sodium hydroxide. The resulting flocculent precipitate was extracted at once with ether, which was then extracted with 5% acetic acid. The acid layer when basified yielded a yellow suspension, which was reextracted with ether. On removal of the solvent, an oil remained which solidified on standing. Melting point 80-95°. Crystallisation from light petroleum (80/100°) yielded yellow rods, which observed on the Köfler apparatus melted at 100-104°. After passage through an activated alumina column in ethanol, the melting point was unchanged. Yield 0.45 gm. (70% of theory.)

Found: C, 74.2; H, 6.6; N, 11.4.

$C_{23}H_{26}ON_4$ requires C, 73.8; H, 6.95; N, 15.0.

$C_{23}H_{26}ON_4.C_{23}H_{25}O_2N_3$ requires

C, 73.6; H, 6.7; N, 11.2.

The significance of these figures is discussed on page 120.

The base is soluble in ethanol and ether, in which it shows a marked blue fluorescence, and in acids, where it exhibits a green fluorescence.

A small portion of the base was dissolved in the minimum amount of ethanol, and to it a saturated solution of 3:5-dinitrobenzoic acid in the same solvent was added. The precipitate which formed was collected and crystallised from ethanol.
Melting point 235°.

Found: C, 55.2; H, 4.2; N, 13.6.

$C_{23}H_{26}O_{14}N_4.2C_7H_4O_6N_2$ requires

C, 55.6; H, 4.2; N, 14.0.

It is thus a bis-dinitrobenzoate, and is yellow in colour.

6'-METHOXY-4-DIETHYLAMINOETHOXY-2:3:4':3'-QUINOQUINOLINE.

6'-Methoxy-4-chloro-2:3:4':3'-quinoquinoline (0.5 gm.) was heated with diethylaminoethanol (5 c.c.) in dry phenol for 4 hours. The reaction mixture was poured into sodium hydroxide (2N), from which the product was extracted with ether. Attempts to extract the base from the ethereal solution with 5% acetic acid were unsuccessful, and it was found necessary to use at least 10% acetic acid. On rendering alkaline with ammonium hydroxide, reextracting with ether, drying and removing the solvent, an oil remained which did not crystallise even on scratching and long standing. The white dinitrobenzoate of the compound was formed, and was found to melt at 103°.

Found: C, 49.8; H, 3.8; N, 11.6.

$C_{23}H_{25}O_2N_3 . 3C_7H_4O_6N_2 . 3H_2O$ requires C, 49.6; H, 4.0; N, 11.8.

The base shows a green fluorescence in ether, and is only sparingly soluble in 5% acetic acid.

THE ATTEMPTED PREPARATION OF 6'-METHOXY-4-(4-DIETHYLAMINO-1-METHYLBUTYLAMINO)-2:3:4':3'-QUINOQUINOLINE.

A mixture of phenol (3 gm.) and 2-amino-5-diethylaminopentane (1.5 gm.) ~~were~~ was dried under vacuum at 100° for one hour. 6'-Methoxy-4-chloro-2:3:-4':3'-quinoquinoline (1 gm.) was added, and the dark red solution heated under reflux at 100° for 4 hours. After cooling, the viscous solution was poured into 2N sodium hydroxide (30 c.c.), and the resulting oily suspension extracted with ether. The ethereal layer was extracted with 5% acetic acid, which was then basified with ammonium hydroxide to give a yellow oil. This was reextracted with ether, the ethereal solution dried and the solvent removed under vacuum. The purified yellow oil solidified on standing to give a yellow solid melting at 91-2°. Crystallisation from light petroleum (60/80°) yielded long, yellow prisms, m.p. 98-100°. Yield 1.1 gm. (72% of theory.)

Found: C, 75.2; H, 7.4; N, 12.2.

$C_{26}H_{32}ON_4$ requires C, 75.0; H, 7.7; N, 13.5.

$C_{26}H_{32}ON_4.C_{26}H_{31}O_2N_3$ req. C, 74.9; H, 7.6; N, 11.8.

The base is very soluble in ethanol and ether, showing a blue fluorescence. The solution of the base in dilute acetic acid (in which it is very soluble) shows a green fluorescence.

THE ATTEMPTED PREPARATION OF 6'-CHLORO-4-DIETHYL-AMINOETHYL-2:3:4':3'-QUINOQUINOLINE.

4:6'-Dichloro-2:3:4':3'-quinoquinoline (0.77 gm.) was heated with dry phenol (5 gm.) and diethylaminoethylamine (0.7 gm.) for 4 hours at 100°; it was allowed to stand at room temperature overnight (convenience). The dark red viscous solution was poured into dilute sodium hydroxide, which was extracted with ether. The ethereal solution was extracted with 5% acetic, which was then basified with ammonium hydroxide to yield the base as a yellow solid. After crystallising repeatedly from light petroleum (80/100°) and drying in a vacuum desiccator over potassium hydroxide, the base softened at 113° and melted at 115-7°.

Found: C, 70.4; H, 5.95; N, 12.8.

$C_{22}H_{23}N_4Cl$ requires C, 69.75; H, 6.1; N, 14.8.

$C_{22}H_{23}N_4Cl.C_{22}H_{22}ON_3Cl$ requires

C, 69.6; H, 5.9; N, 12.9.

The base is soluble in ether and light petroleum, exhibiting a deep blue fluorescence. It is very soluble in dilute acids, but insoluble in alkali.

THE ATTEMPTED PREPARATION OF 6'-CHLORO-4-(4-DIETHYLAMINO-1-METHYLBUTYLAMINO)-2:3:4':3'-QUINOQUINOLINE.

A mixture of dry phenol (3 gm.), 2-amino-5-diethylaminopentane (1.5 gm.) and 4:6'-dichloro-2:3:4':3'-quinoquinoline (1 gm.) were heated under reflux at 100° for 4 hours. When cold, the viscous solution was basified with sodium hydroxide and extracted with ether. The ethereal layer was extracted with 5% acetic acid, from which the base was liberated with ammonium hydroxide. After reextraction with ether, and removal of the solvent, the base was left as a yellow oil, which on treatment with light petroleum (60/80°) eventually solidified. Melting point 75-80°. Crystallisation from light petroleum (60/80°) yielded the base as pale yellow cubes, melting at 78-80°.

Found: C, 70.8; H, 6.7; N, 12.25.

$C_{25}H_{29}N_4Cl$ requires C, 71.35; H, 6.9; N, 13.3.

$C_{25}H_{29}N_4Cl.C_{25}H_{28}ON_3Cl$ requires

C, 71.2; H, 6.8; N, 11.6.

The base is soluble in ethanol, methanol and light petroleum; im these solvents it shows a blue fluorescence. It is very readily soluble in dilute acetic acid.

THE ATTEMPTED PREPARATION OF 6'-METHOXY-4-AMINO-2:3:4':3'-QUINOQUINOLINE.

cf. Albert and Ritchie, J.Soc. Chem. Ind., 1941, 60, 120.

6'-Methoxy-4-chloro-2:3:4':3'-quinoquinoline (0.5 gm.) was heated at 70° with dry, freshly distilled phenol (0.5 gm.) till complete solution was obtained. Ammonium carbonate (A.R.) (0.4 gm.) was then added as quickly as the effervescence would allow, and the temperature raised to 120° as rapidly as possible. After one hour's heating, the dark solution was cooled, diluted with water and made strongly alkaline with sodium hydroxide. The yellow precipitate which resulted was filtered, washed and dried. Melting point 260-80°. It was partially soluble in 5% acetic acid, with which it was extracted by warming on the water bath; the residue melted at 330-40°. The filtrate on basification with ammonium hydroxide yielded a small amount of an orange gelatinous substance, melting at 290-300°, and which was soluble in ethanol and benzene with a marked blue fluorescence. In an attempt to purify it, this orange material was passed through a column of activated alumina while dissolved in benzene. No separation into bands occurred, the material passing right through as a diffuse,

yellow band. The melting point of the recovered material was 305°.

The higher melting material, (330-40°), was found to dissolve in more concentrated acetic acid (10%), from which it was reprecipitated as a gel with ammonium hydroxide. It dissolved readily in hot ethanol, but always separated as a gel on cooling. It was thought to be the phenoxy compound.

As chromatography and crystallisation did not sharpen the melting point of the lower melting material, which was obtained in very poor yield on both occasions, the method was discarded; the procedure described below was more successful.

6'-Methoxy-4-chloro-2:3:4':3'-quinoquinoline (1 gm.) was dissolved in dry, freshly distilled phenol (3gm.) by gentle heating in an oil bath. Ammonia gas, dried over soda lime, was bubbled into the phenolic solution for 1½ hours, the temperature being maintained at 100-120°. On cooling, the dark green solution was diluted with water and basified with sodium hydroxide to yield an oil, which on scratching solidified to a yellow, amorphous material. After filtering, the filtrate was set aside whilst the solid was well washed with water, dissolved in dilute acetic acid (5%), and precipitated with ammonium hydroxide. Melting point ca. 300°. The base

after five crystallisations from ethanol melted at 312-4°. Yield 0.5 gm. (55% of theory.)

Found: C, 74.4; H, 4.6; N, 12.5.

$C_{17}H_{13}ON_3$ requires C, 74.2; H, 4.7; N, 15.3.

$C_{17}H_{13}ON_3.C_{17}H_{12}O_2N_2$ requires

C, 74.05; H, 4.5; N, 12.7.

The results are discussed on page 125.

The base is insoluble in water, acetone, benzene and alkali, but is soluble in nitrobenzene and in ethanol and methanol; these last two solutions exhibit a very marked blue fluorescence at extreme dilutions. Its solution in acetic acid shows a green fluorescence.

On long standing, the filtrate set aside, yielded a gelatinous precipitate which melted at 310-20°. It dissolved in strong acetic acid, from which it was precipitated by ammonium hydroxide. M.P. 330°. It was identical with the higher melting material, thought to be the 5-phenoxy compound described in the previous experiment.

6'-METHOXY-4-AMINO-2:3:4':3'-QUINOQUINOLINE METHIODIDE.

The previously prepared base (0.2 gm.) was dissolved in nitrobenzene with warming, and cooled. Methyl iodide (10 c.c.) was added, and the whole was heated on a boiling water bath for 9 hours. After standing at room temperature overnight, the precipitate (which began to separate within the first five minutes of heating) was filtered off, washed with ether and dried. M.P. 290-300°. On crystallisation from nitrobenzene, the yellow crystals of the monomethiodide of 6'-methoxy-4-amino-2:3:4':3'-quinoquinoline were found to melt at 314-5°, and to turn red on standing.

Found: C, 52.1; H, 4.05; N, 10.0.

$C_{17}H_{13}ON_3.CH_3I$ requires C, 51.8; H, 3.85; N, 10.0.

An aqueous solution of the methiodide yields an orange anhydronium base, m.p. 110°, on treatment with alkali.

THE ATTEMPTED PREPARATION OF 6'-CHLORO-4-AMINO-2:3:4':3'-QUINOQUINOLINE.

4:6'-Dichloro-2:3:4':3'-quinoquinoline (1 gm.) dissolved in phenol (3 gm.) was heated at 110-20° for one hour, during which time dry ammonia gas was bubbled into the solution. When cold, the dark green solution was diluted with water and made strongly alkaline with sodium hydroxide. The precipitate was filtered, washed and dried. For purification, it was extracted with dilute acetic acid, treated with decolourising charcoal, filtered, and the filtrate basified with ammonium hydroxide to give a clear, yellow, crystalline product. After repeated crystallisations from ethanol, the base was found to melt at >300°.

Found: C, 68.6; H, 3.8; N, 12.4.

$C_{23}H_{10}N_3Cl$ requires C, 68.7; H, 3.8; N, 15.0.

$C_{23}H_{10}N_3Cl.C_{23}H_9ON_2Cl$ requires

C, 68.5; H, 3.4; N, 12.5.

The base shows an intense blue fluorescence in ethanol.

A small amount of material which was insoluble in acetic acid was found to be 6'-chloro-2:3:4':3'-quinoquinolo-4-one.

SUMMARY

1. From diethylethoxymethylene malonate and the appropriate aniline, 4-chloroquinoline, 6-methoxy-4-chloroquinoline and 4:6-dichloroquinoline have been prepared.

2. These chloro compounds have been used in the synthesis of 2:3-benz-γ-carboline, 15-methoxy-2:3-benz-γ-carboline and 15-chloro-2:3-benz-γ-carboline. The unambiguous synthesis of the former base has cleared up certain discrepancies which existed in the literature.

3. The 2:3-benz-γ-carbolines have been treated with diethylaminoethyl chloride to obtain basic side chain derivatives. In this way, the following have been prepared:

1-diethylaminoethyl-2:3-benz-γ-carboline.

4-diethylaminoethyl-2:3-benz-γ-isocarboline.

15-methoxy-4-diethylaminoethyl-2:3-benz-γ-isocarboline.

15-chloro-1-diethylaminoethyl-2:3-benz-γ-carboline.

15-chloro-4-diethylaminoethyl-2:3-benz-γ-isocarboline.

In addition, 4-methyl-2:3-benz-γ-isocarboline and 15-chloro-4-methyl-2:3-benz-γ-isocarboline were also prepared.

4. The constitution of 1-diethylaminoethyl-2:3-benz-γ-carboline (and by analogy, of the corresponding 15-methoxy- and 15-chloro- compounds) has been established from a study of its methiodides.

5. The synthesis of 2:3:4':3'-quinoquinolo-4-one, 6'-methoxy-2:3:4':3'-quinoquinolo-4-one, 6'-chloro-2:3:4':3'-quinoquinolo-4-one, and of 4-chloro-2:3:4':3'-quinoquinoline, 6'-methoxy-4-chloro-2:3:4':3'-quinoquinoline and 4:6'-dichloro-2:3:4':3'-quinoquinoline from the corresponding 4-anilinoquinoline-3-carboxylic acids, has been described. These compounds are isomeric with the 5-chloropyridoacridines, which they resemble markedly in properties.

6. From the above chloroquinoquinolines, bases have been obtained by condensing them with amines such as ammonia, diethylaminoethylamine and 2-amino-5-diethylaminopentane. The constitution of the products obtained is still uncertain.

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